

1 ***Supporting Information for***

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4 **Synthesis and Evaluation of Halogenated**
5 **5-(2-Hydroxyphenyl)pyrazoles as Pseudolin Analogues Targeting the**
6 **Enzyme IspD in the MEP Pathway**

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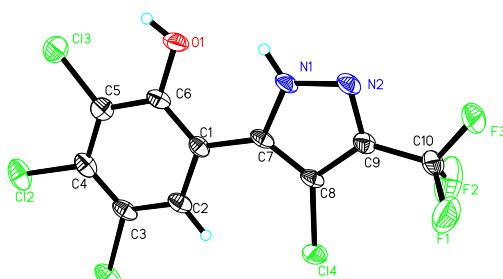
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38 1. Table S1. X-ray crystal structure of compound **6c** and single crystal data

39



Name	Value
Empirical formula	C ₁₀ H ₃ Cl ₄ F ₃ N ₂ O
Formula weight	365.94
Temperature	296(2) K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	P-1
Unit cell dimensions	a = 7.553(3) Å α = 64.713(6)°. b = 8.979(4) Å β = 84.956(6)°. c = 10.372(4) Å γ = 77.125(5)°.
Volume	620.0(4) Å ³
Z	2
Density (calculated)	1.960 Mg/m ³
Absorption coefficient	0.986 mm ⁻¹
F(000)	360
Crystal size	0.120 x 0.100 x 0.100 mm ³
Theta range for data collection	2.172 to 25.999°.
Index ranges	-9<=h<=9, -11<=k<=10, -12<=l<=12
Reflections collected	4246
Independent reflections	2363 [R(int) = 0.0665]
Completeness to theta = 25.242°	97.1 %
Absorption correction	None
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	2363 / 0 / 182
Goodness-of-fit on F ²	1.053
Final R indices [I>2sigma(I)]	R1 = 0.0607, wR2 = 0.1603
R indices (all data)	R1 = 0.0704, wR2 = 0.1713
Extinction coefficient	n/a
Largest diff. peak and hole	0.784 and -0.692 e.Å ⁻³

40 **2. AtIspD expression and inhibition activity assay**

41 The cloning and expression of *AtIspD* (gene fragment 76-302) was performed
42 according to a reported method, and with it, a high-throughput screening protocol was
43 established. The protocol follows the principle that *AtIspD* catalyzes cytidilation of
44 MEP to CDP-ME in coupling with pyrophosphatase and releases monophosphate.
45 Monophosphate reacts with the malachite green-ammonium molybdate complex, and
46 the color change can be colorimetrically monitored to determine the *AtIspD* activity.
47 To do this, a buffer reaction system was first made, which contained 1.0 mM DTT,
48 1.0 mM MgCl₂, 0.5 mM CTP, 0.1 U inorganic pyrophosphatase, and 89.7 μM *AtIspD*
49 protein in 100 mM Tris-HCl buffer solution (pH = 7.5), and then allotted to a 96-well
50 plate with 30 μL in each well and the solutions of inhibitors in DMSO ranging from
51 0.01 to 100 μM were separately added to the wells. Next, the substrate MEP dissolved
52 in 100 mM Tris-HCl buffer (pH = 7.5) was added to each well with a final
53 concentration of 0.5 mM to initiate the reaction. After incubation for 10 min at 37 °C,
54 the reaction was quenched with 1.0 M HClO₄, followed by adding 450 μL mixed
55 solution of 0.045 % malachite green and 4.2 % ammonium molybdate (v/v 3: 1) to
56 develop the color reaction. The absorbance at 620 nm was measured by the
57 SpectraMax M5 microplate reader, and the inhibition curve was plotted and fitted for
58 each inhibitor to obtain the IC₅₀ value. Each experiment was triplicated and the
59 average value reported.

60 **3. Model plant inhibition activity assay**

61 The pre-emergence inhibition activity was determined on model plants including
62 monocotyledon barnyard grass and dicotyledon rape with the standard Petri dish test.
63 The compounds were dissolved in DMF and emulsified with Tween-80, and the
64 solutions were diluted with water to a concentration of 1000 mg/L, named concentrate
65 solutions, parts of which were further diluted to a gradient of 100, 50, 25, 10 and 1
66 mg/L for use. The solutions of the references pentabromo pseudilin and PIX were also
67 made as the positive controls. The test solutions of 9 mL were added to Petri dishes (9
68 cm diameter) lined with a filter paper on which 10–15 seeds of each of the two model
69 plants were placed. The growth culture was performed in the incubator with a
70 humidity of 75% at 25 °C, in which first in the dark for 3 days then in the alternating
71 light (10 Klux) and dark for 12 h/day each till for 5 days. The inhibition rates were
72 calculated using the equation E = (C-T)/C × 100%, where E is the inhibition rate of
73 the root or stalk, C and T are the root or stalk lengths of the blank control and the
74 group treated with the test solution, respectively. Each target compound was assayed
75 for the growth inhibition on root and stalk of the model plants using five
76 concentrations as a gradient, and the effective concentration with an inhibitory
77 activity of 50% was calculated, expressed as EC₅₀. For the complete list of all the
78 target compounds and their EC₅₀ values (Table S2), the test was triplicated and
79 average values reported.

80

81 **4.Table S2.** EC₅₀ values of target compounds against model plants

Compounds	EC ₅₀ (mg/L)			
	Rape		Barnyard grass	
	root	stalk	root	stalk
5a	5.76 ± 0.11	7.71 ± 0.18	11.91 ± 0.21	<1
5b	9.22 ± 0.17	28.78 ± 0.31	2.53 ± 0.08	3.59 ± 0.28
5c	22.49 ± 0.36	49.96 ± 0.87	10.43 ± 0.25	3.59 ± 0.12
5d	>100	>100	11.51 ± 0.24	14.09 ± 0.17
5e	5.97 ± 0.26	>100	29.11 ± 0.59	2.26 ± 0.19
5f	2.81 ± 0.05	9.75 ± 0.09	9.65 ± 0.25	1.38 ± 0.16
5g	13.89 ± 0.41	>100	11.58 ± 0.87	12.03 ± 0.62
5h	>100	>100	24.22 ± 0.55	27.35 ± 0.22
5j	5.19 ± 0.13	>100	6.92 ± 0.12	9.33 ± 0.27
5k	27.45 ± 0.32	40.47 ± 0.37	25.50 ± 0.48	12.26 ± 0.10
5l	11.16 ± 0.14	>100	23.87 ± 0.78	27.23 ± 0.17
5m	18.75 ± 0.17	>100	24.42 ± 0.52	18.55 ± 0.28
5n	15.98 ± 0.28	>100	25.66 ± 0.36	4.33 ± 0.13
5o	2.48 ± 0.09	13.71 ± 0.51	5.62 ± 0.31	15.17 ± 0.57
5p	11.06 ± 0.40	>100	22.79 ± 0.12	11.28 ± 0.61
5q	34.19 ± 0.39	>100	3.41 ± 0.06	22.69 ± 0.19
6a	21.49 ± 0.58	11.38 ± 0.28	2.48 ± 0.09	6.92 ± 0.15
6b	10.63 ± 0.13	21.16 ± 0.25	8.35 ± 0.11	<1
6c	9.75 ± 0.18	27.45 ± 0.64	9.43 ± 0.08	2.58 ± 0.12
6d	2.36 ± 0.08	22.46 ± 0.08	2.53 ± 0.17	<1
6e	28.00 ± 0.68	>100	11.16 ± 0.16	24.74 ± 0.33
6f	3.34 ± 0.21	24.52 ± 2.68	16.70 ± 0.27	4.74 ± 0.20
6g	3.44 ± 0.19	28.10 ± 0.63	23.44 ± 0.29	27.88 ± 0.16
6h	59.94 ± 1.68	>100	22.79 ± 0.16	29.41 ± 0.25
6j	17.57 ± 0.51	>100	10.08 ± 0.07	1.28 ± 0.17
6k	3.46 ± 0.21	15.19 ± 0.61	7.25 ± 0.41	2.58 ± 0.15
6l	10.45 ± 0.35	28.98 ± 0.49	10.33 ± 0.30	3.22 ± 0.02
6m	15.72 ± 0.25	20.51 ± 0.53	3.11 ± 0.07	3.34 ± 0.07
6n	30.46 ± 0.10	>100	15.22 ± 0.16	25.88 ± 0.68
6o	11.28 ± 0.19	19.43 ± 0.65	31.16 ± 0.55	25.72 ± 0.53
6p	<1	>100	34.62 ± 0.51	14.52 ± 0.28
6q	38.22 ± 0.71	>100	19.88 ± 0.23	28.95 ± 0.16
Pseudolin	7.25 ± 0.13	11.69 ± 0.41	14.61 ± 0.23	2.09 ± 0.12
PIX	9.26 ± 0.32	10.08 ± 0.30	12.58 ± 0.15	1.59 ± 0.08

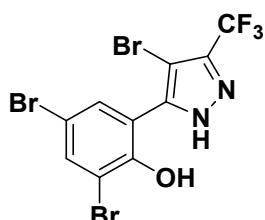
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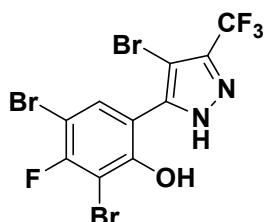
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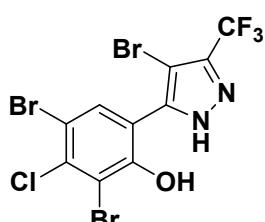
86 **5.** Chemical structures, physical properties, and the data of ^1H NMR, ^{13}C NMR, and
87 HRMS of compounds **5a-h**, **5j-q**, **6a-h**, **6j-q**



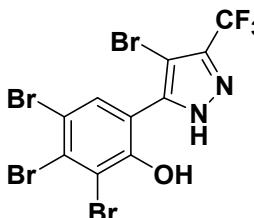
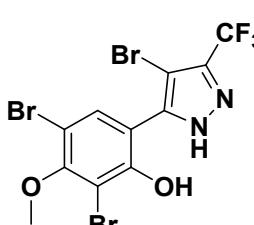
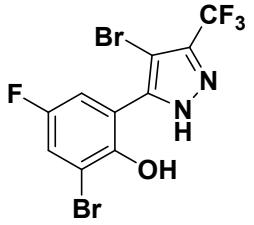
89 *4-Bromo-5-(3,5-dibromo-2-hydroxyphenyl)-3-trifluoromethyl-1H-pyrazole* (**5a**):
90 Yield: 88%. Light yellow solid. m.p. 194.3-195.1 °C. ^1H NMR (600 MHz, DMSO- d_6)
91 δ 14.26 (s, 1H), 10.16 (s, 1H), 7.93 (s, 1H), 7.56 (s, 1H). ^{13}C NMR (150 MHz,
92 DMSO- d_6) δ 151.7, 138.9, 136.2, 133.0, 121.1 (d, J = 268.8 Hz), 118.6, 113.2, 110.8,
93 91.9. ^{19}F NMR (376 MHz, DMSO- d_6) δ -56.07 (s). HRMS (Dual ESI): Calcd for
94 C₁₀H₄Br₃F₃N₂O [M-H]⁻ 460.7753. Found 460.7756.

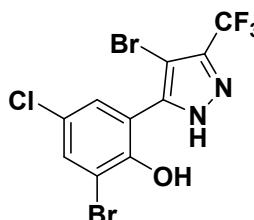


96 *4-Bromo-5-(3,5-dibromo-4-fluoro-2-hydroxyphenyl)-3-trifluoromethyl-1H-pyrazole*
97 (**5b**): Yield: 78%. Brown solid. m.p. 182.2-183.5 °C. ^1H NMR (600 MHz, DMSO- d_6)
98 δ 14.26 (s, 1H), 10.72 (s, 1H), 7.76 (d, J = 7.8 Hz, 1H). ^{13}C NMR (150 MHz,
99 DMSO- d_6) δ 156.4 (d, J = 245.2 Hz), 153.8, 138.5, 133.7 (d, J = 14.0 Hz), 121.17 (d,
100 J = 269.0 Hz), 114.17, 100.77 (d, J = 23.0 Hz), 97.87 (d, J = 23.2 Hz), 92.2. ^{19}F NMR
101 (376 MHz, DMSO- d_6) δ -56.08 (s), -89.66 (s). HRMS (Dual ESI): Calcd for
102 C₁₀H₄Br₃F₄N₂O [M-H]⁻ 479.7737. Found 479.7730.

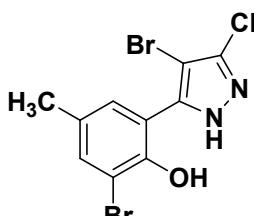


104 *4-Bromo-5-(4-chloro-3,5-dibromo-2-hydroxyphenyl)-3-trifluoromethyl-1H-pyrazole*
105 (**5c**): Yield: 76%. Light yellow solid. m.p. 192.5-193.8 °C. ^1H NMR (600 MHz,
106 DMSO- d_6) δ 14.28 (s, 1H), 10.57 (s, 1H), 7.82 (s, 1H). ^{13}C NMR (150 MHz,
107 DMSO- d_6) δ 153.2, 138.4, 135.8, 133.8, 121.1 (d, J = 269.4 Hz), 116.7, 114.37,
108 111.5, 92.1. ^{19}F NMR (376 MHz, DMSO- d_6) δ -56.06 (s). HRMS (Dual ESI): Calcd
109 for C₁₀H₃Br₃ClF₃N₂O [M-H]⁻ 494.7363. Found 494.7359.

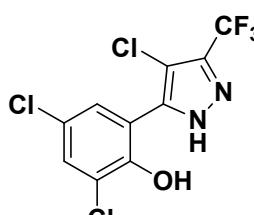
- 110 
- 111 **4-Bromo-5-(3,4,5-tribromo-2-hydroxyphenyl)-3-trifluoromethyl-1H-pyrazole (5d):**
 112 Yield: 82%. White solid. m.p. 208.9-209.8 °C. ¹H NMR (600 MHz, DMSO-d₆) δ
 113 14.22 (s, 1H), 10.54 (s, 1H), 7.81 (s, 1H). ¹³C NMR (150 MHz, DMSO-d₆) δ 152.8,
 114 138.6, 133.7, 129.4, 121.1 (d, J = 269.0 Hz), 117.1, 116.9, 114.0, 92.1. ¹⁹F NMR (376
 115 MHz, DMSO-d₆) δ -56.05 (s). HRMS (Dual ESI): Calcd for C₁₀H₃Br₄F₃N₂O [M-H]⁻
 116 538.6858. Found 538.6851.
- 117 
- 118 **4-Bromo-5-(3,5-dibromo-4-methoxy-2-hydroxyphenyl)-3-trifluoromethyl-1H-pyrazole (5e):**
 119 Yield: 89%. Light yellow solid. m.p. 202.6-203.9 °C. ¹H NMR (600 MHz, DMSO-d₆) δ 14.20 (s, 1H), 10.22 (s, 1H), 7.65 (d, J = 1.1 Hz, 1H), 3.85 (s, 3H). ¹³C NMR (150 MHz, DMSO-d₆) δ 155.6, 153.3, 138.8, 133.4, 121.2 (d, J = 269.4 Hz), 114.1, 108.9, 106.4, 91.9, 60.4. ¹⁹F NMR (376 MHz, DMSO-d₆) δ -56.08 (s). HRMS (Dual ESI): Calcd for C₁₁H₆Br₃F₃N₂O₂ [M-H]⁻ 490.7859. Found 490.7865.
- 124 
- 125 **4-Bromo-5-(3-bromo-5-fluoro-2-hydroxyphenyl)-3-trifluoromethyl-1H-pyrazole (5f):**
 126 Yield: 66%. Claybank solid. m.p. 146.7-147.9 °C. ¹H NMR (600 MHz, DMSO-d₆) δ
 127 14.28 (s, 1H), 9.88 (s, 1H), 7.71 (dd, J = 7.8, 2.8 Hz, 1H), 7.33 (dd, J = 8.4, 2.8 Hz,
 128 1H). ¹³C NMR (150 MHz, DMSO-d₆) δ 154.7 (d, J = 240.6 Hz), 148.9, 139.3, 121.4
 129 (d, J = 25.6 Hz), 121.2 (d, J = 268.0 Hz), 117.5 (d, J = 8.4 Hz), 117.25 (d, J = 23.8
 130 Hz), 112.4 (d, J = 10.6 Hz), 91.7. ¹⁹F NMR (376 MHz, CDCl₃) δ -62.46 (s), -119.40
 131 (s). HRMS (Dual ESI): Calcd for C₁₀H₄Br₂F₄N₂O [M-H]⁻ 400.8554. Found
 132 400.8561.

133 

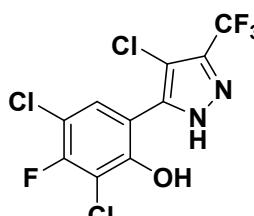
134 *4-Bromo-5-(3-bromo-5-chloro-2-hydroxyphenyl)-3-trifluoromethyl-1H-pyrazole (5g):*
 135 Yield: 68%. Light yellow solid. m.p. 178.8-179.9 °C. ¹H NMR (600 MHz, DMSO-*d*₆)
 136 δ 14.29 (s, 1H), 10.13 (s, 1H), 7.84 (s, 1H), 7.46 (s, 1H). ¹³C NMR (150 MHz,
 137 DMSO-*d*₆) δ 151.3, 139.0, 133.7, 130.27, 123.7, 121.1 (d, J = 268.6 Hz), 118.1,
 138 112.8, 91.9. ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ -60.82 (s). HRMS (Dual ESI): Calcd
 139 for C₁₀H₄Br₂ClF₃N₂O [M-H]⁻ 416.8258. Found 416.8249.

140 

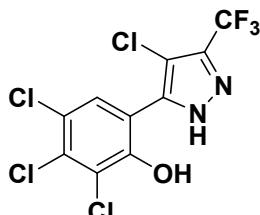
141 *4-Bromo-5-(3-bromo-5-methyl-2-hydroxyphenyl)-3-trifluoromethyl-1H-pyrazole (5h):*
 142 Yield: 58%. Light yellow solid. m.p. 166.4-167.6 °C. ¹H NMR (400 MHz, DMSO-*d*₆)
 143 δ 14.16 (s, 1H), 9.50 (s, 1H), 7.53 (s, 1H), 7.14 (s, 1H), 2.26 (s, 3H). ¹³C NMR
 144 (100 MHz, DMSO-*d*₆) δ 149.6, 140.3, 139.0 (d, J = 35.8 Hz), 134.8, 131.1, 130.4,
 145 121.3 (d, J = 268.8 Hz), 116.8, 111.8, 91.3, 19.5. ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ
 146 -60.83 (s). HRMS (Dual ESI): Calcd for C₁₁H₇Br₂F₃N₂O [M-H]⁻ 396.8805. Found
 147 396.8813.

148 

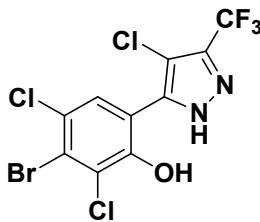
149 *4-Chloro-5-(3,5-dichloro-2-hydroxyphenyl)-3-trifluoromethyl-1H-pyrazole (6a):*
 150 Yield: 65%. White solid. m.p. 194.5-196.1 °C. ¹H NMR (600 MHz, DMSO-*d*₆) δ
 151 14.24 (s, 1H), 10.40 (s, 1H), 7.72 (d, J = 2.4 Hz, 1H), 7.47 (d, J = 2.4 Hz, 1H). ¹³C
 152 NMR (150 MHz, DMSO-*d*₆) δ 150.3, 137.0, 130.8, 129.4, 123.4, 122.9, 121.0 (d, J =
 153 268.8 Hz), 117.6, 106.6. ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ -56.19 (s). HRMS (Dual
 154 ESI): Calcd for C₁₀H₄Cl₃F₃N₂O [M-H]⁻ 328.9269. Found 328.9261.

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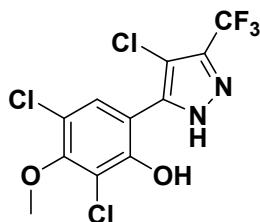
156 *4-Chloro-5-(3,5-dichloro-4-fluoro-2-hydroxyphenyl)-3-trifluoromethyl-1H-pyrazole*
 157 (**6b**): Yield: 68%. White solid. m.p. 184.6-185.8 °C. ¹H NMR (600 MHz, DMSO-*d*₆)
 158 δ 14.22 (s, 1H), 10.98 (s, 1H), 7.67 (dd, *J* = 8.1, 3.2 Hz, 1H). ¹³C NMR (150 MHz,
 159 DMSO-*d*₆) δ 154.7 (d, *J* = 249.6 Hz), 152.2, 136.6, 130.0, 121.0 (d, *J* = 268.6 Hz),
 160 112.9, 111.1 (d, *J* = 18.4 Hz), 110.9 (d, *J* = 18.2 Hz), 106.8. ¹⁹F NMR (376 MHz,
 161 DMSO-*d*₆) δ -56.23 (s), -106.20 (s). HRMS (Dual ESI): Calcd for C₁₀H₃Cl₃F₄N₂O
 162 [M-H]⁻ 346.9174. Found 346.9172.



163
 164 *4-Chloro-5-(3,4,5-trichloro-2-hydroxyphenyl)-3-trifluoromethyl-1H-pyrazole* (**6c**):
 165 Yield: 60%. Yellow solid. m.p. 210.1-211.8°C. ¹H NMR (400 MHz, DMSO-*d*₆) δ
 166 14.30 (s, 1H), 10.86 (s, 1H), 7.74 (s, 1H). ¹³C NMR (150 MHz, DMSO-*d*₆) δ 151.5,
 167 136.5, 132.3, 129.9, 122.7, 122.5, 121.0 (d, *J* = 269.0 Hz), 115.8, 106.9. ¹⁹F NMR
 168 (376 MHz, DMSO-*d*₆) δ -56.21 (s). HRMS (Dual ESI): Calcd for C₁₀H₃Cl₄F₃N₂O
 169 [M-H]⁻ 362.8879. Found 362.8873.

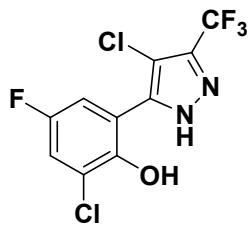


170
 171 *4-Chloro-5-(4-bromo-3,5-dichloro-2-hydroxyphenyl)-3-trifluoromethyl-1H-pyrazole*
 172 (**6d**): Yield: 60%. Light yellow solid. m.p. 214.7-215.8 °C. ¹H NMR (600 MHz, DMSO-*d*₆)
 173 δ 14.30 (s, 1H), 10.79 (s, 1H), 7.71 (s, 1H). ¹³C NMR (150 MHz, DMSO-*d*₆) δ 151.1, 136.6, 129.8, 125.0, 124.8, 124.5, 121.0 (d, *J* = 269.0 Hz), 116.3,
 174 106.8. ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ -56.19 (s). HRMS (Dual ESI): Calcd for
 175 C₁₀H₃BrCl₃F₃N₂O [M-H]⁻ 406.8374. Found 406.8371.



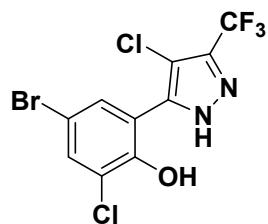
177
 178 *4-Chloro-5-(3,5-dichloro-4-methoxy-2-hydroxyphenyl)-3-trifluoromethyl-1H-pyrazole*
 179 (**6e**): Yield: 71%. White solid. m.p. 169.3-170.4 °C. ¹H NMR (600 MHz, DMSO-*d*₆) δ
 180 14.19 (s, 1H), 10.43 (s, 1H), 7.54 (d, *J* = 4.3 Hz, 1H), 3.88 (s, 3H). ¹³C NMR (150
 181 MHz, DMSO-*d*₆) δδ 153.6, 151.7, 137.0, 130.0, 121.0 (d, *J* = 269.2 Hz), 118.1, 117.8,
 182 112.7, 106.5, 60.6. ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ -56.21 (s). HRMS (Dual ESI):

183 Calcd for C₁₁H₆Cl₃F₃N₂O₂ [M-H]⁻ 358.9374 Found 358.9369.



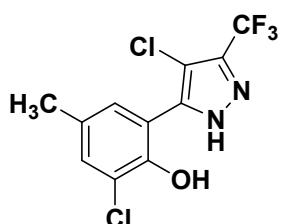
184

185 *4-Chloro-5-(3-chloro-5-fluoro-2-hydroxyphenyl)-3-trifluoromethyl-1H-pyrazole (6f):*
186 Yield: 51%. Claybank solid. m.p. 148.8-150.1 °C. ¹H NMR (400 MHz, DMSO-d₆) δ
187 14.26 (s, 1H), 9.99 (s, 1H), 7.62 (s, 1H), 7.34 (s, 1H). ¹³C NMR (100 MHz,
188 DMSO-d₆) δ 154.5 (d, J = 239.4 Hz), 147.9, 147.9, 137.2, 122.5 (d, J = 11.4 Hz),
189 121.0 (d, J = 268.8 Hz), 118.6 (d, J = 26.0 Hz), 116.9 (d, J = 9.6 Hz), 116.4 (d, J =
190 23.8 Hz), 106.5. ¹⁹F NMR (376 MHz, DMSO-d₆) δ -60.93 (s), -122.38 (s). HRMS
191 (Dual ESI): Calcd for C₁₀H₄Cl₂F₄N₂O [M-H]⁻ 312.9564. Found 312.9558.



192

193 *4-Chloro-5-(5-bromo-3-chloro-2-hydroxyphenyl)-3-trifluoromethyl-1H-pyrazole (6g):*
194 Yield: 60%. Light yellow solid. m.p. 204.8-205.9 °C. ¹H NMR (600 MHz, DMSO-d₆)
195 δ 14.22 (s, 1H), 10.38 (s, 1H), 7.83 (s, 1H), 7.57 (s, 1H). ¹³C NMR (150 MHz,
196 DMSO-d₆) δ 150.7, 136.9, 133.49, 132.2, 123.2, 121.0 (d, J = 268.8 Hz), 118.08,
197 110.48, 106.68. ¹⁹F NMR (376 MHz, DMSO-d₆) δ -60.91 (s). HRMS (Dual ESI):
198 Calcd for C₁₀H₄BrCl₂F₃N₂O [M-H]⁻ 372.8763. Found 372.8770.



199

200 *4-Chloro-5-(3-chloro-5-methoxy-2-hydroxyphenyl)-3-trifluoromethyl-1H-pyrazole
(6h):* Yield: 50%. Light yellow solid. m.p. 157.3-158.4 °C. ¹H NMR (400 MHz,
201 DMSO-d₆) δ 14.16 (s, 1H), 9.72 (s, 1H), 7.39 (s, 1H), 7.15 (s, 1H), 2.26 (s, 3H). ¹³C
202 NMR (150 MHz, DMSO-d₆) δ 148.7, 138.3, 137.2 (d, J = 37.0 Hz), 131.8 (d, J = 28.2
203 Hz), 129.9, 121.5, 121.1 (d, J = 269.2 Hz), 116.1, 106.0. ¹⁹F NMR (376 MHz,
204 DMSO-d₆) δ -60.95 (s). HRMS (Dual ESI): Calcd for C₁₁H₇Cl₂F₃N₂O [M-H]⁻
205 308.9815. Found 308.9806.

207

208 *4-Bromo-5-(3,5-dibromo-2-hydroxyphenyl)-3-difluoromethyl-1H-pyrazole (5j)*: Yield:
209 60%. Light yellow solid. m.p. 215.2-216.8 °C. ¹H NMR (400 MHz, DMSO-*d*₆) δ
210 13.89 (s, 1H), 10.06 (s, 1H), 7.91 (d, *J* = 2.3 Hz, 1H), 7.53 (s, 1H), 7.07 (t, *J* = 53.2
211 Hz, 1H). ¹³C NMR (150 MHz, DMSO-*d*₆) δ 151.7, 143.2, 138.0, 135.9, 132.8, 119.2,
212 113.2, 110.8, 91.7. ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ -113.43 (s). HRMS (Dual ESI):
213 Calcd for C₁₀H₅Br₃F₂N₂O [M-H]⁻ 442.7847. Found 442.7837.

214

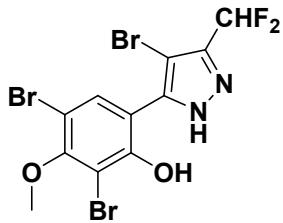
215 *4-Bromo-5-(3,5-dibromo-4-fluoro-2-hydroxyphenyl)-3-difluoromethyl-1H-pyrazole
(5k)*: Yield: 59%. Light yellow solid. m.p. 198.3-199.5 °C. ¹H NMR (600 MHz,
216 DMSO-*d*₆) δ 13.89 (s, 1H), 10.63 (s, 1H), 7.71 (d, *J* = 7.6 Hz, 1H), 7.07 (t, *J* = 52.7
217 Hz, 1H). ¹³C NMR (150 MHz, DMSO-*d*₆) δ 156.3 (d, *J* = 244.4 Hz), 153.7, 143.2,
218 137.6, 133.5, 114.8, 100.7 (d, *J* = 20.8 Hz), 97.8 (d, *J* = 22.8 Hz), 91.9. ¹⁹F NMR (376
219 MHz, DMSO-*d*₆) δ -94.79 (s), -113.43 (s). HRMS (Dual ESI): Calcd for
220 C₁₀H₄Br₃F₃N₂O [M-H]⁻ 460.7753. Found 460.7758.

222

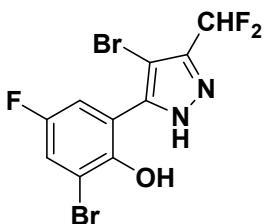
223 *4-Bromo-5-(4-chloro-3,5-dibromo-2-hydroxyphenyl)-3-difluoromethyl-1H-pyrazole
(5l)*: Yield: 58%. Light yellow solid. m.p. 202.1-203.3 °C. ¹H NMR (600 MHz,
224 DMSO-*d*₆) δ 13.95 (s, 1H), 10.52 (s, 1H), 7.78 (s, 1H), 7.08 (t, *J* = 52.9 Hz, 1H). ¹³C
225 NMR (150 MHz, DMSO-*d*₆) δ 153.2, 143.2, 137.7, 135.5, 133.6, 117.4, 114.3, 113.2
226 – 108.9 (m), 111.5, 92.0. ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ -113.42 (s). HRMS (Dual
227 ESI): Calcd for C₁₀H₄Br₃ClF₂N₂O [M-H]⁻ 476.7458. Found 476.7452.

229

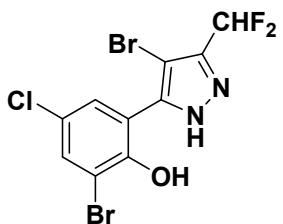
230 **4-Bromo-5-(3,4,5-tribromo-2-hydroxyphenyl)-3-difluoromethyl-1*H*-pyrazole (5m):**
 231 Yield: 50%. Light yellow solid. m.p. 223.0-224.2 °C. ¹H NMR (600 MHz, DMSO-*d*₆)
 232 δ 13.96 (s, 1H), 10.45 (s, 1H), 7.77 (s, 1H), 7.07 (t, *J* = 53.3 Hz, 1H). ¹³C NMR (100
 233 MHz, DMSO-*d*₆) δ 152.8, 142.4, 138.3, 133.5, 128.9, 117.9, 116.9, 114.0, 111.2 (t, *J*
 234 = 232.8 Hz), 91.9. ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ -113.50 (s). HRMS (Dual ESI):
 235 Calcd for C₁₀H₄Br₄F₂N₂O [M-H]⁻ 520.6952. Found 520.6959.



236 **4-Bromo-5-(3,5-dibromo-4-methoxy-2-hydroxyphenyl)-3-difluoromethyl-1*H*-pyrazole (5n):** Yield: 79%. Light yellow solid. m.p. 217.6-218.9 °C. ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.87 (s, 1H), 10.18 (s, 1H), 7.62 (s, 1H), 7.06 (t, *J* = 53.2 Hz, 1H), 3.84 (s, 3H). ¹³C NMR (100 MHz, DMSO-*d*₆) δ 155.3, 153.3, 133.2, 114.8, 111.3 (t, *J* = 237.4 Hz), 108.8, 106.3, 91.7, 60.4. ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ -113.50 (s). HRMS (Dual ESI): Calcd for C₁₁H₇Br₃F₂N₂O₂ [M-H]⁻ 472.7953. Found 472.7958.

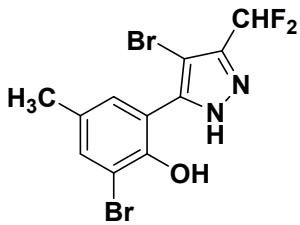


243 **4-Bromo-5-(3-bromo-5-fluoro-2-hydroxyphenyl)-3-difluoromethyl-1*H*-pyrazole (5o):**
 244 Yield: 55%. White solid. m.p. 170.5-171.9 °C. ¹H NMR (600 MHz, DMSO-*d*₆) δ
 245 13.94 (s, 1H), 9.73 (s, 1H), 7.68 (d, *J* = 5.6 Hz, 1H), 7.31 (d, *J* = 6.9 Hz, 1H), 7.07 (t,
 246 *J* = 53.1 Hz, 1H). ¹³C NMR (150 MHz, DMSO-*d*₆) δ 154.8 (d, *J* = 235.6 Hz), 148.9,
 247 138.5, 121.1 (d, *J* = 26.4 Hz), 118.2, 116.9, 112.4, 111.3, 91.6. ¹⁹F NMR (376 MHz,
 248 DMSO-*d*₆) δ -113.25 (s), -122.50 (s). HRMS (Dual ESI): Calcd for C₁₀H₅Br₂F₃N₂O
 249 [M-H]⁻ 382.8648. Found 382.8629.



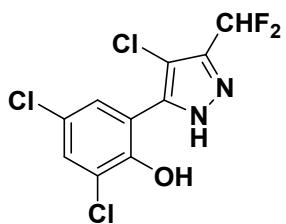
251 **4-Bromo-5-(3-bromo-5-chloro-2-hydroxyphenyl)-3-difluoromethyl-1*H*-pyrazole (5p):**
 252 Yield: 49%. Light yellow solid. m.p. 194.0-195.7 °C. ¹H NMR (400 MHz, DMSO-*d*₆)
 253 δ 13.93 (s, 1H), 10.06 (s, 1H), 7.82 (s, 1H), 7.42 (s, 1H), 7.06 (t, *J* = 53.0 Hz, 1H). ¹³C
 254 NMR (150 MHz, DMSO-*d*₆) δ 151.3, 143.2, 138.3, 133.33, 130.03, 123.7, 118.8,

256 112.88, 111.4, 91.7. ^{19}F NMR (376 MHz, DMSO- d_6) δ -113.41 (s). HRMS (Dual ESI):
257 Calcd for $\text{C}_{10}\text{H}_5\text{Br}_2\text{ClF}_2\text{N}_2\text{O} [\text{M}-\text{H}]^-$ 398.8353. Found 398.8361.



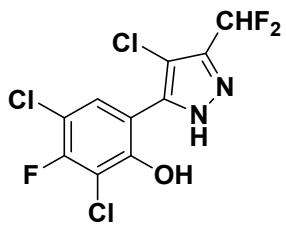
258

259 *4-Bromo-5-(3-bromo-5-methyl-2-hydroxyphenyl)-3-difluoromethyl-1H-pyrazole (5q):*
260 Yield: 58%. Light yellow solid. m.p. 167.5-168.9 °C. ^1H NMR (400 MHz, DMSO- d_6)
261 δ 13.86 (s, 1H), 9.49 (s, 1H), 7.55 (s, 1H), 7.12 (dd, $J = 71.0, 35.2$ Hz, 1H), 2.31 (s,
262 3H). ^{13}C NMR (150 MHz, DMSO- d_6) δ 149.6, 143.1, 139.5, 134.5, 131.0, 130.3,
263 117.4, 114.9, 111.8, 91.2, 19.6. ^{19}F NMR (376 MHz, DMSO- d_6) δ -113.32 (s). HRMS
264 (Dual ESI): Calcd for $\text{C}_{11}\text{H}_8\text{Br}_2\text{F}_2\text{N}_2\text{O} [\text{M}-\text{H}]^-$ 378.8899. Found 378.8889.



265

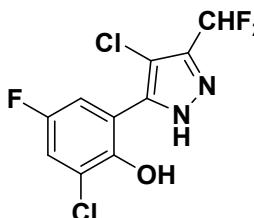
266 *4-Chloro-5-(3,5-dichloro-2-hydroxyphenyl)-3-difluoromethyl-1H-pyrazole (6j):*
267 Yield: 52%. Light yellow solid. m.p. 171.0-171.9 °C. ^1H NMR (400 MHz, DMSO- d_6)
268 δ 13.89 (s, 1H), 10.28 (s, 1H), 7.71 (s, 1H), 7.43 (s, 1H), 7.09 (t, $J = 52.9$ Hz, 1H). ^{13}C
269 NMR (150 MHz, DMSO- d_6) δ 150.3, 141.6, 136.26, 130.46, 129.36, 123.36, 122.9,
270 118.2, 106.4. ^{19}F NMR (376 MHz, DMSO- d_6) δ -113.78 (s). HRMS (Dual ESI):
271 Calcd for $\text{C}_{10}\text{H}_5\text{Cl}_3\text{F}_2\text{N}_2\text{O} [\text{M}-\text{H}]^-$ 310.9363. Found 310.9361.



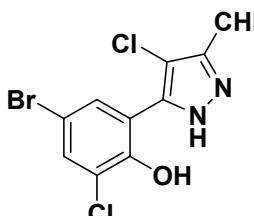
272

273 *4-Chloro-5-(3,5-dichloro-4-fluoro-2-hydroxyphenyl)-3-difluoromethyl-1H-pyrazole*
274 (**6k**): Yield: 62%. Light pink solid. m.p. 181.1-182.8 °C. ^1H NMR (400 MHz,
275 DMSO- d_6) δ 13.89 (s, 1H), 10.96 (s, 1H), 7.63 (d, $J = 8.2$ Hz, 1H), 7.10 (t, $J = 53.0$
276 Hz, 1H). ^{13}C NMR (150 MHz, DMSO- d_6) δ 158.1 (d, $J = 249.4$ Hz), 156.0 (d, $J =$
277 10.4 Hz), 152.14, 136.0, 131.64, 111.94, 109.14 (d, $J = 18.2$ Hz), 105.7, 104.6 (d, $J =$
278 23.2 Hz). ^{19}F NMR (376 MHz, DMSO- d_6) δ -112.11 (s), -113.76 (s). HRMS (Dual
279 ESI) : Calcd for $\text{C}_{10}\text{H}_4\text{Cl}_3\text{F}_3\text{N}_2\text{O} [\text{M}-\text{H}]^-$ 328.9269. Found 328.9257.

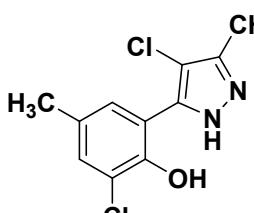
- 280
-
- 281 *4-Chloro-5-(3,4,5-trichloro-2-hydroxyphenyl)-3-difluoromethyl-1H-pyrazole (6l):*
- 282 Yield: 58%. Light yellow solid. m.p. 148.9-150.4 °C. ¹H NMR (600 MHz, DMSO-*d*₆) δ 13.95 (s, 1H), 10.70 (s, 1H), 7.67 (s, 1H), 7.11 (t, *J* = 54.0 Hz, 1H). ¹³C NMR (100 MHz, DMSO-*d*₆) δ 154.9, 151.1, 135.7 (t, *J* = 612.4 Hz), 131.2, 124.7 (d, *J* = 33.6 Hz), 123.0 (d, *J* = 20.4 Hz), 120.7, 115.3, 111.3 (t, *J* = 232.6 Hz), 105.8. ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ -113.79 (s). HRMS (Dual ESI): Calcd for C₁₀H₄Cl₄F₂N₂O [M-H]⁻ 344.8973. Found 344.8982.
- 288
-
- 289 *4-Chloro-5-(4-bromo-3,5-dichloro-2-hydroxyphenyl)-3-difluoromethyl-1H-pyrazole (6m):* Yield: 61%. Light yellow solid. m.p. 169.8-171.4 °C. ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.93 (s, 1H), 10.73 (s, 1H), 7.67 (s, 1H), 7.11 (t, *J* = 52.8 Hz, 1H). ¹³C NMR (100 MHz, DMSO-*d*₆) δ 154.9, 151.1, 135.7 (t, *J* = 612.4 Hz), 131.2, 124.7 (d, *J* = 33.6 Hz), 123.0 (d, *J* = 20.4 Hz), 120.7, 115.3, 111.3 (t, *J* = 232.6 Hz), 105.8. ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ -113.79 (s). HRMS (Dual ESI): Calcd for C₁₀H₄BrCl₃F₂N₂O [M-H]⁻ 388.8468. Found 388.8463.
- 296
-
- 297 *4-Chloro-5-(3,5-dichloro-4-methoxy-2-hydroxyphenyl)-3-difluoromethyl-1H-pyrazole (6n):* Yield: 69%. Light yellow solid. m.p. 187.6-188.9 °C. ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.85 (s, 1H), 10.41 (s, 1H), 7.51 (s, 1H), 7.10 (t, *J* = 53.2 Hz, 1H), 3.87 (s, 3H). ¹³C NMR (100 MHz, DMSO-*d*₆) δ 155.3, 153.25, 133.2, 114.8, 111.3, 108.8, 106.3, 91.7, 60.4. ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ -113.50 (s). HRMS (Dual ESI): Calcd for C₁₁H₇Cl₃F₂N₂O₂ [M-H]⁻ 340.9468. Found 340.9473.



 303
 304 *4-Chloro-5-(3-chloro-5-fluoro-2-hydroxyphenyl)-3-trifluoromethyl-1H-pyrazole (6o):*
 305 Yield: 63%. White solid. m.p. 163.9–165.2 °C. ^1H NMR (400 MHz, DMSO- d_6) δ 13.91 (s, 1H), 9.95 (s, 1H), 7.57 (dd, J = 8.1, 2.8 Hz, 1H), 7.31 (d, J = 8.4 Hz, 1H),
 306 7.11 (t, J = 53.0 Hz, 1H). ^{13}C NMR (100 MHz, DMSO- d_6) δ 154.5 (d, J = 239.4 Hz),
 307 147.9, 141.6, 136.4, 122.5 (d, J = 11.6 Hz), 118.2 (d, J = 25.2 Hz), 117.6, 116.2 (d, J =
 308 27.0 Hz), 111.3, 106.3. ^{19}F NMR (376 MHz, DMSO- d_6) δ -113.80 (s), -122.44 (s).
 309 HRMS (Dual ESI): Calcd for $\text{C}_{10}\text{H}_5\text{Cl}_2\text{F}_3\text{N}_2\text{O} [\text{M}-\text{H}]^-$ 294.9658. Found 294.9651.



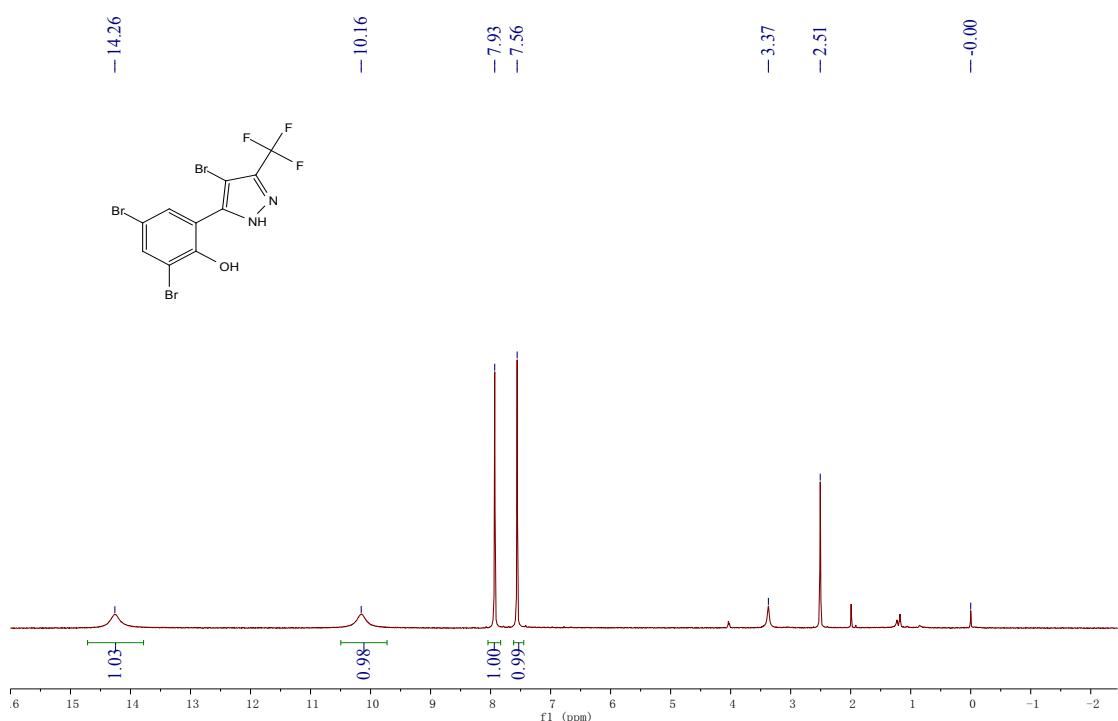
 311
 312 *4-Chloro-5-(5-bromo-3-chloro-2-hydroxyphenyl)-3-difluoromethyl-1H-pyrazole (6p):*
 313 Yield: 58%. White solid. m.p. 188.7–190.0 °C. ^1H NMR (400 MHz, DMSO- d_6) δ 13.89
 314 (s, 1H), 10.31 (s, 1H), 7.80 (s, 1H), 7.53 (s, 1H), 7.10 (t, J = 52.4 Hz, 1H). ^{13}C NMR
 315 (150 MHz, DMSO- d_6) δ 150.7, 141.8, 136.1, 133.1, 132.0, 123.2, 118.7, 110.4, 106.4.
 316 ^{19}F NMR (376 MHz, DMSO- d_6) δ -113.75 (s). HRMS (Dual ESI): Calcd for
 317 $\text{C}_{10}\text{H}_5\text{BrCl}_2\text{F}_2\text{N}_2\text{O} [\text{M}-\text{H}]^-$ 354.8858. Found 354.8862.



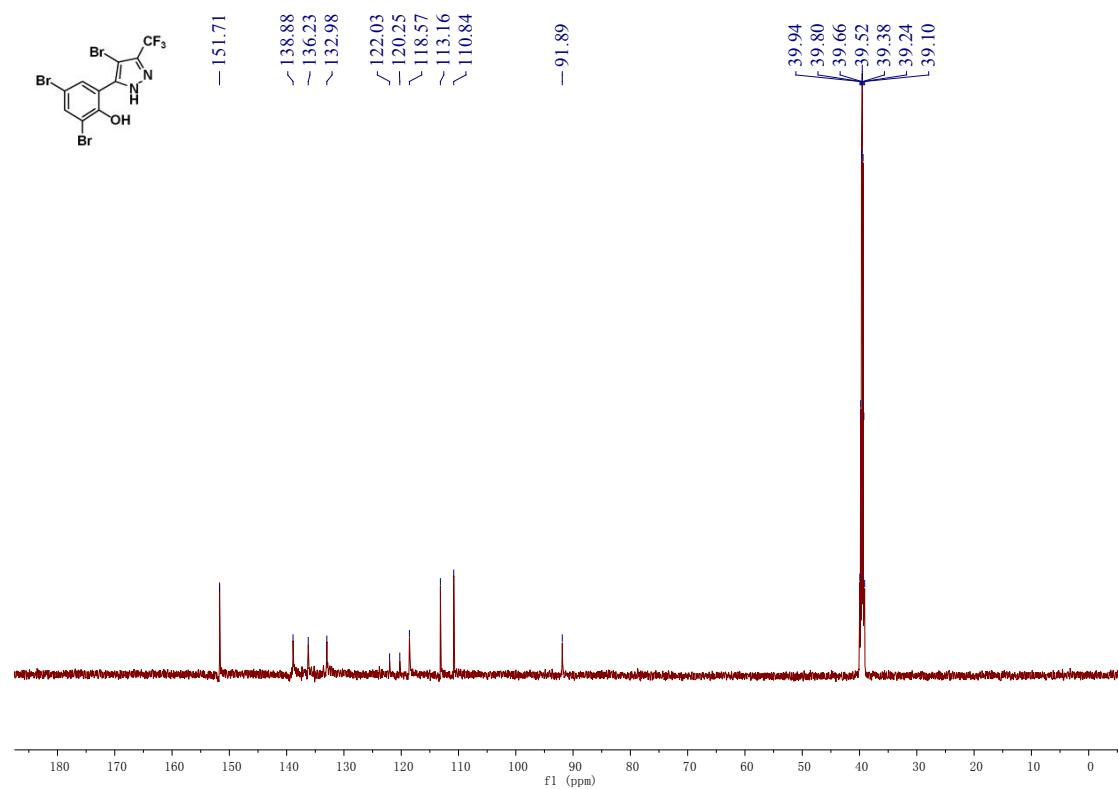
 318
 319 *4-Chloro-5-(3-chloro-5-methyl-2-hydroxyphenyl)-3-difluoromethyl-1H-pyrazole (6q):*
 320 Yield: 53%. Light yellow solid. m.p. 163.5–165.9 °C. ^1H NMR (400 MHz, DMSO- d_6)
 321 δ 7.82 (d, J = 2.8 Hz, 1H), 7.68 (d, J = 2.4 Hz, 1H), 7.11 (t, J = 52.8 Hz, 1H), 1.99 (s,
 322 3H). ^{13}C NMR (150 MHz, DMSO- d_6) δ 149.6, 143.1, 139.5, 134.5, 131.0, 130.3,
 323 117.4, 114.9, 111.8, 91.2, 19.6. ^{19}F NMR (376 MHz, DMSO- d_6) δ -113.32 (s). HRMS
 324 (Dual ESI): Calcd for $\text{C}_{11}\text{H}_8\text{Cl}_2\text{F}_2\text{N}_2\text{O} [\text{M}-\text{H}]^-$ 290.9909. Found 290.9901.

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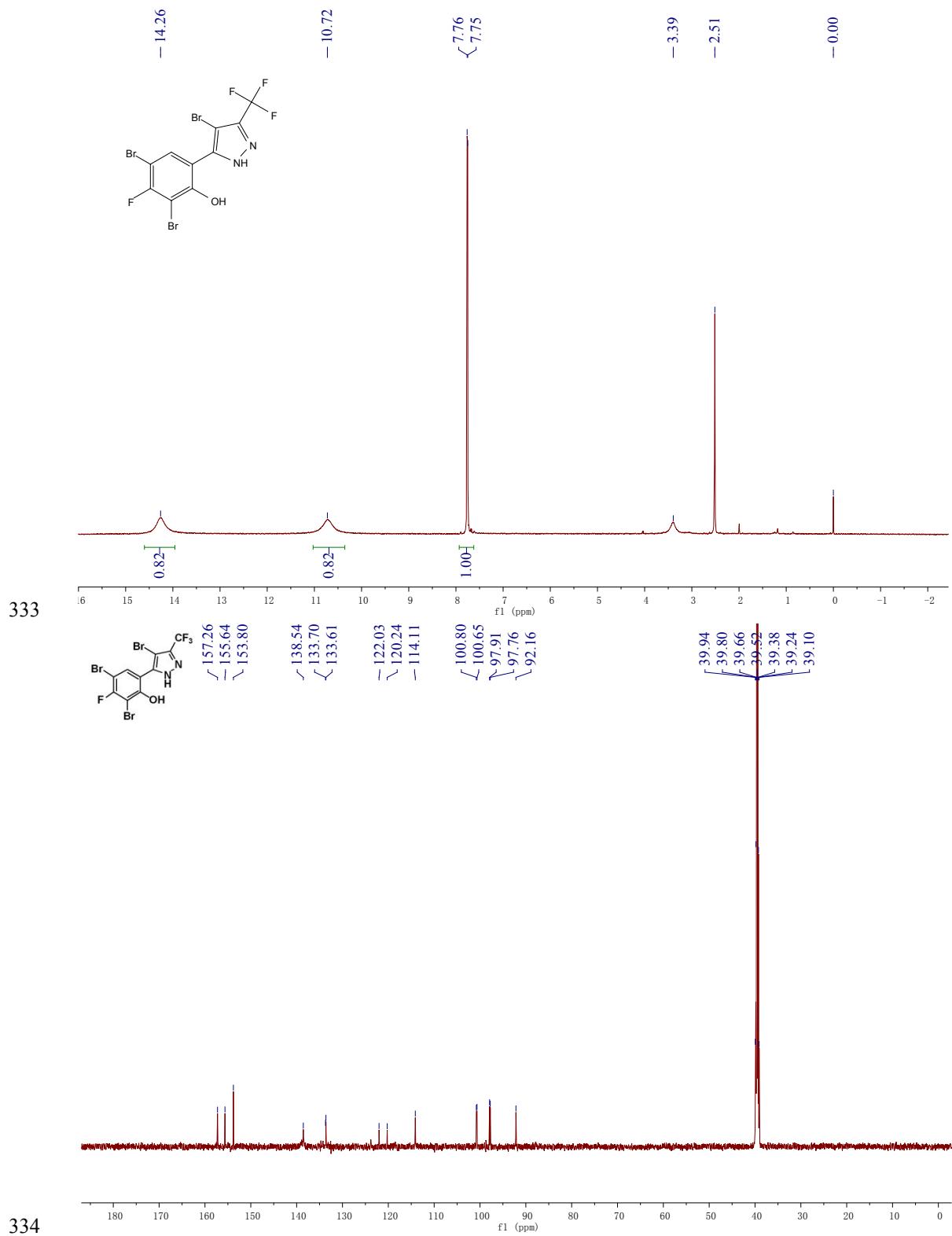
330 **6. Spectra of ^1H NMR, ^{13}C NMR of compounds 5a-h, 5j-q, 6a-h, 6j-q**

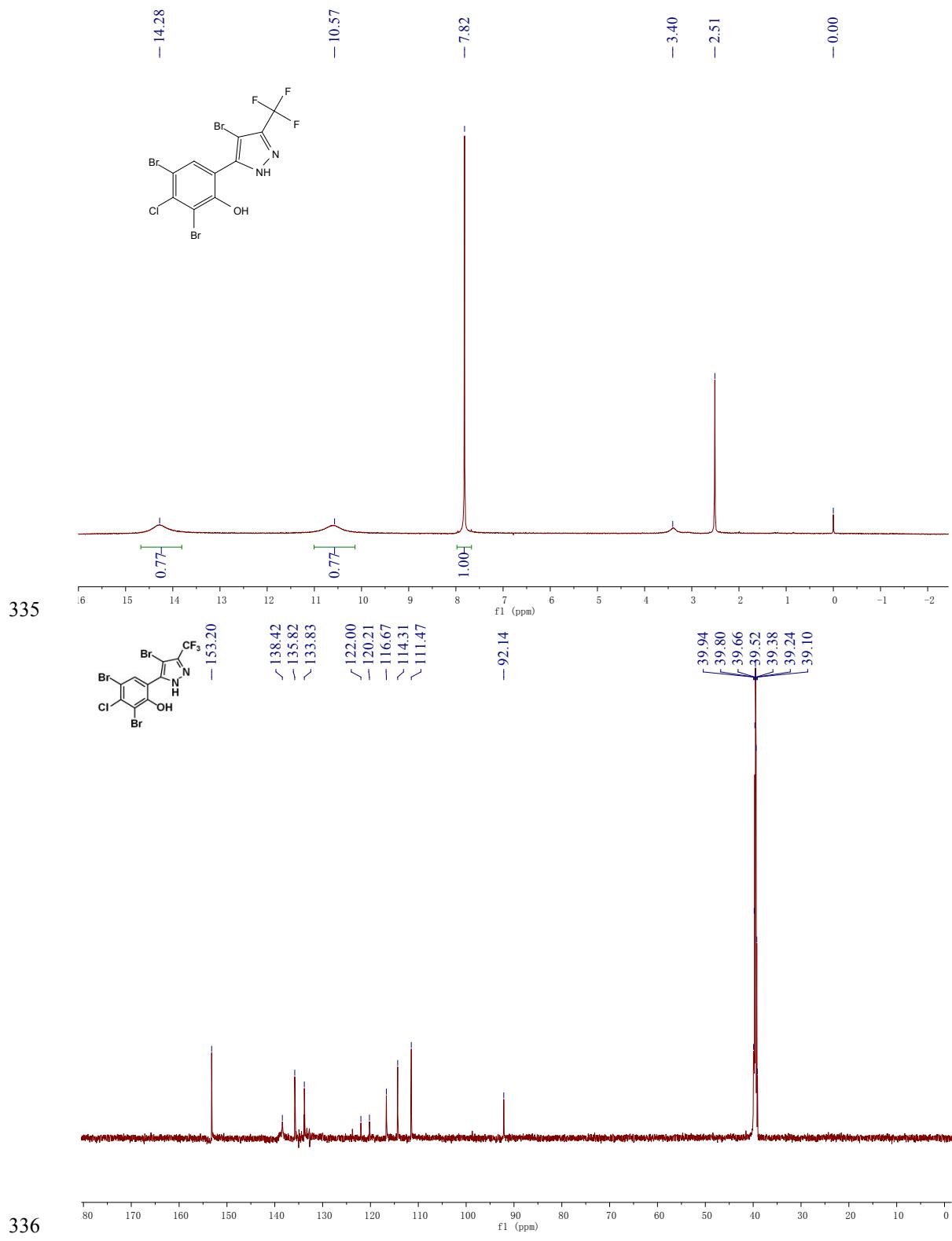


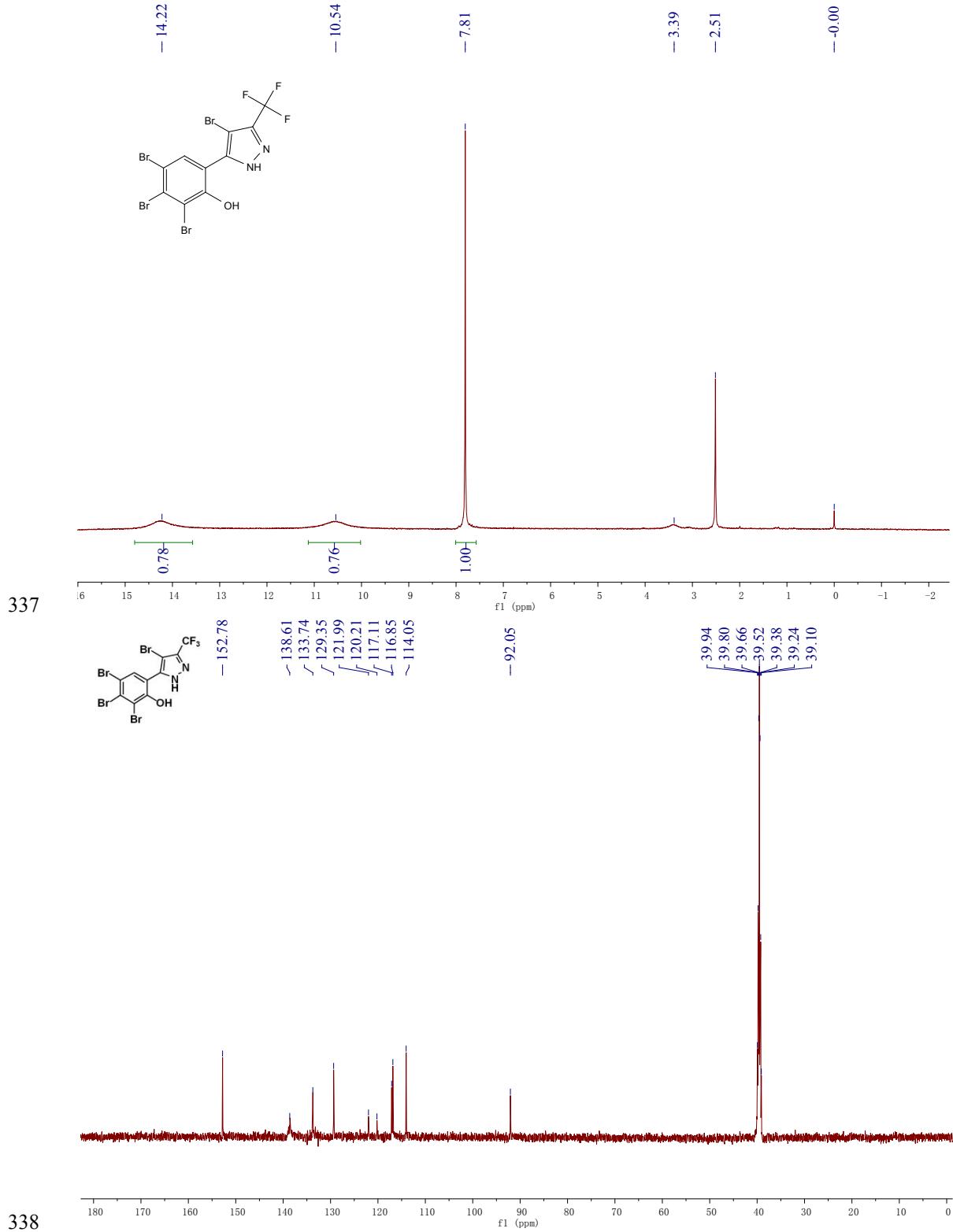
331



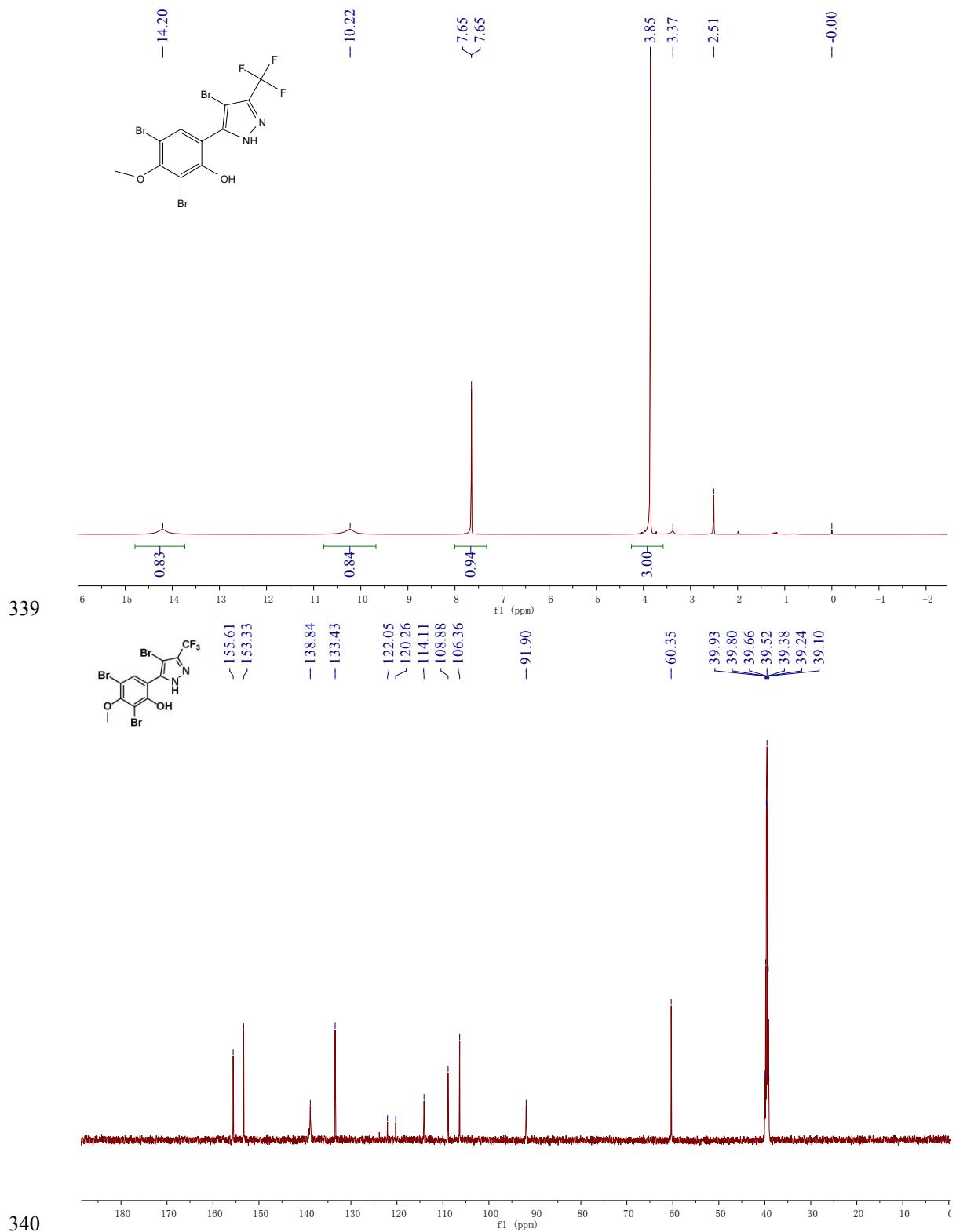
332

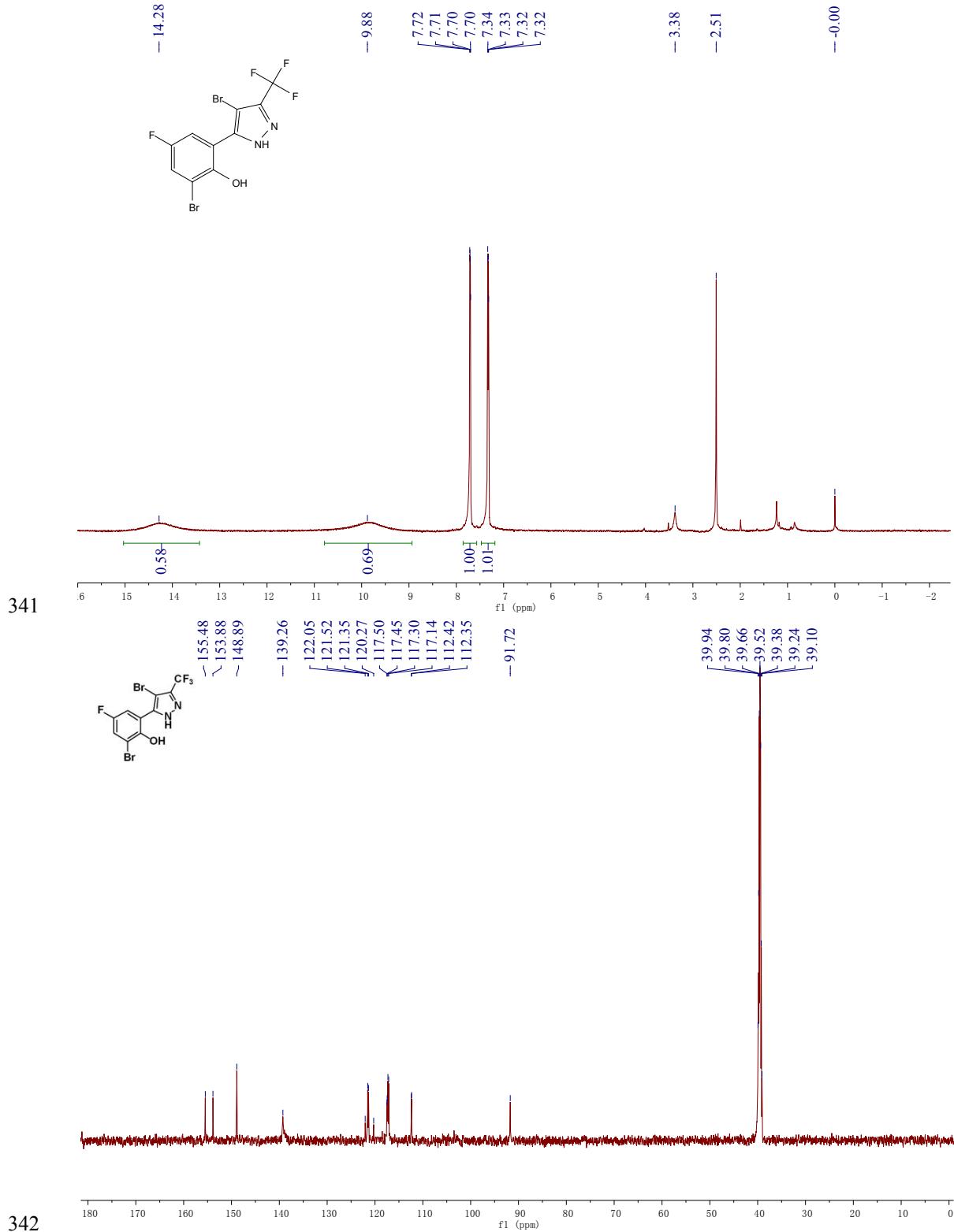


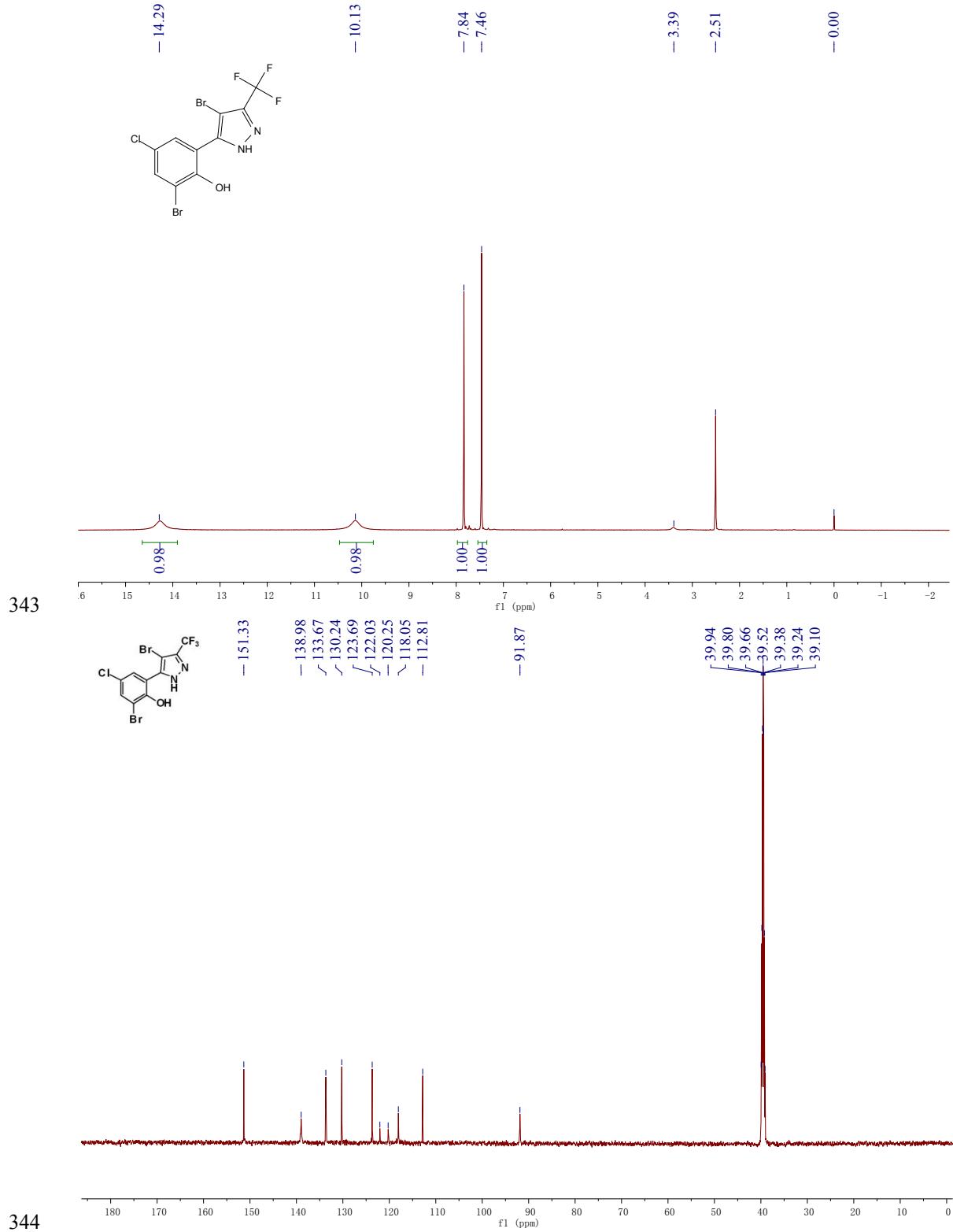


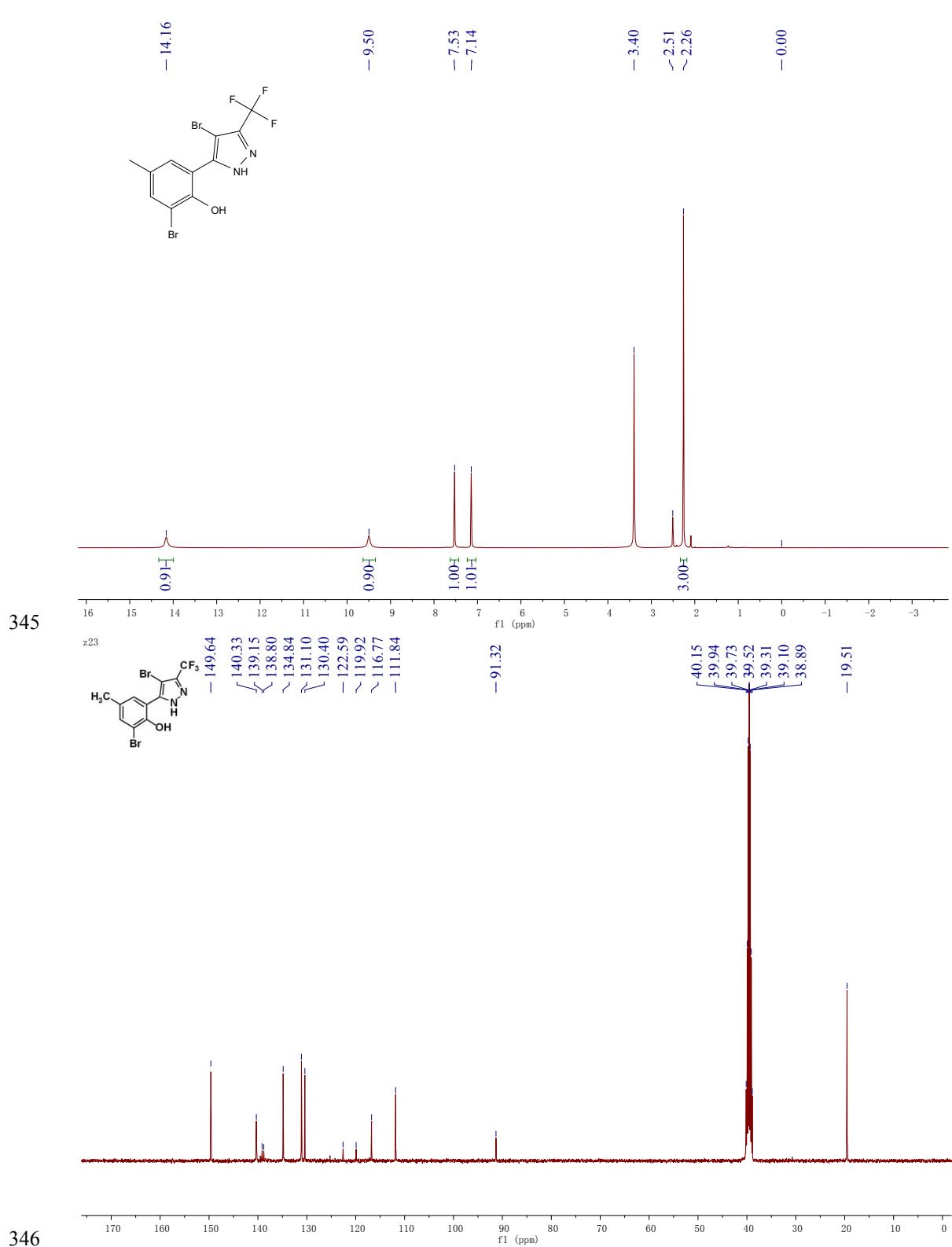


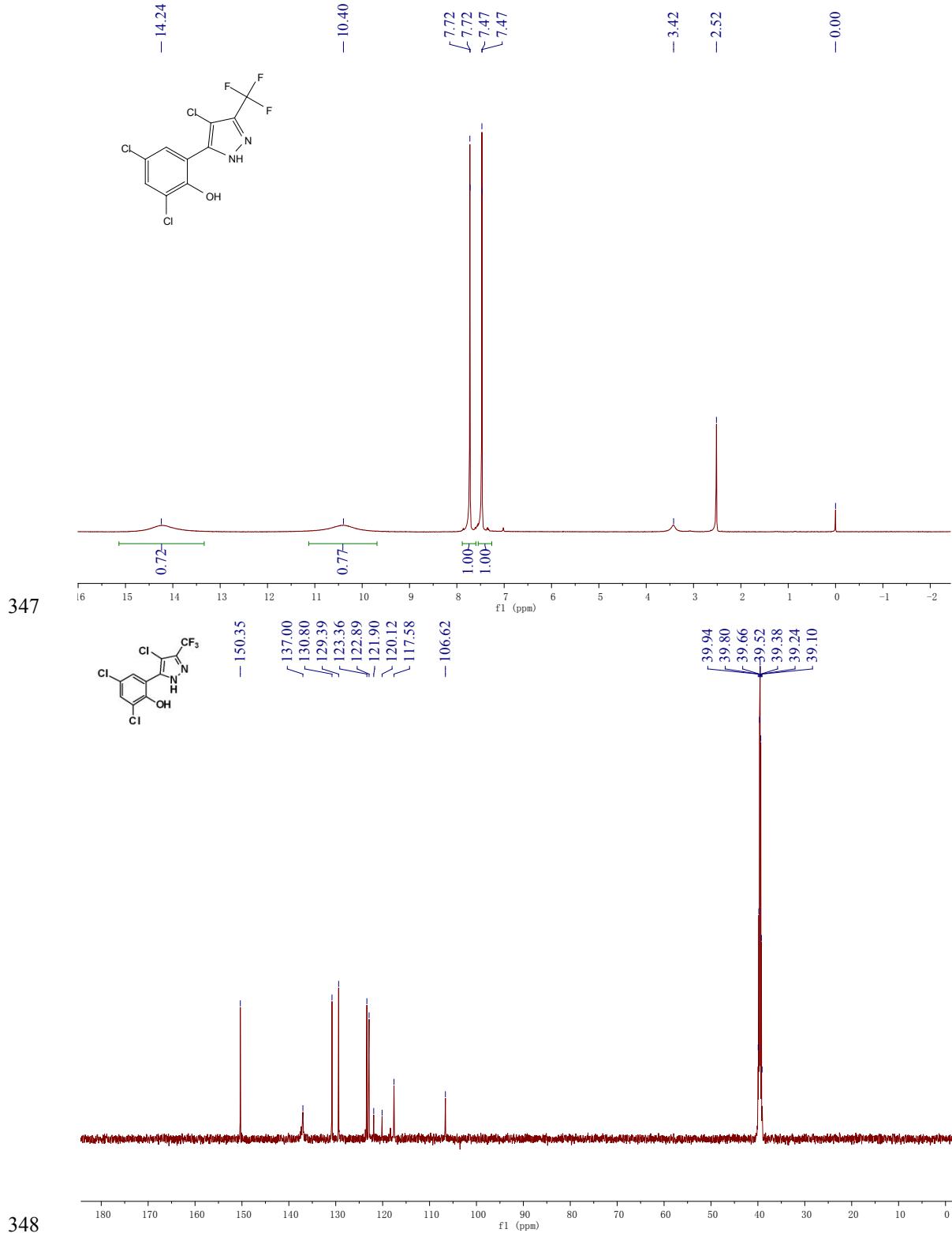
338

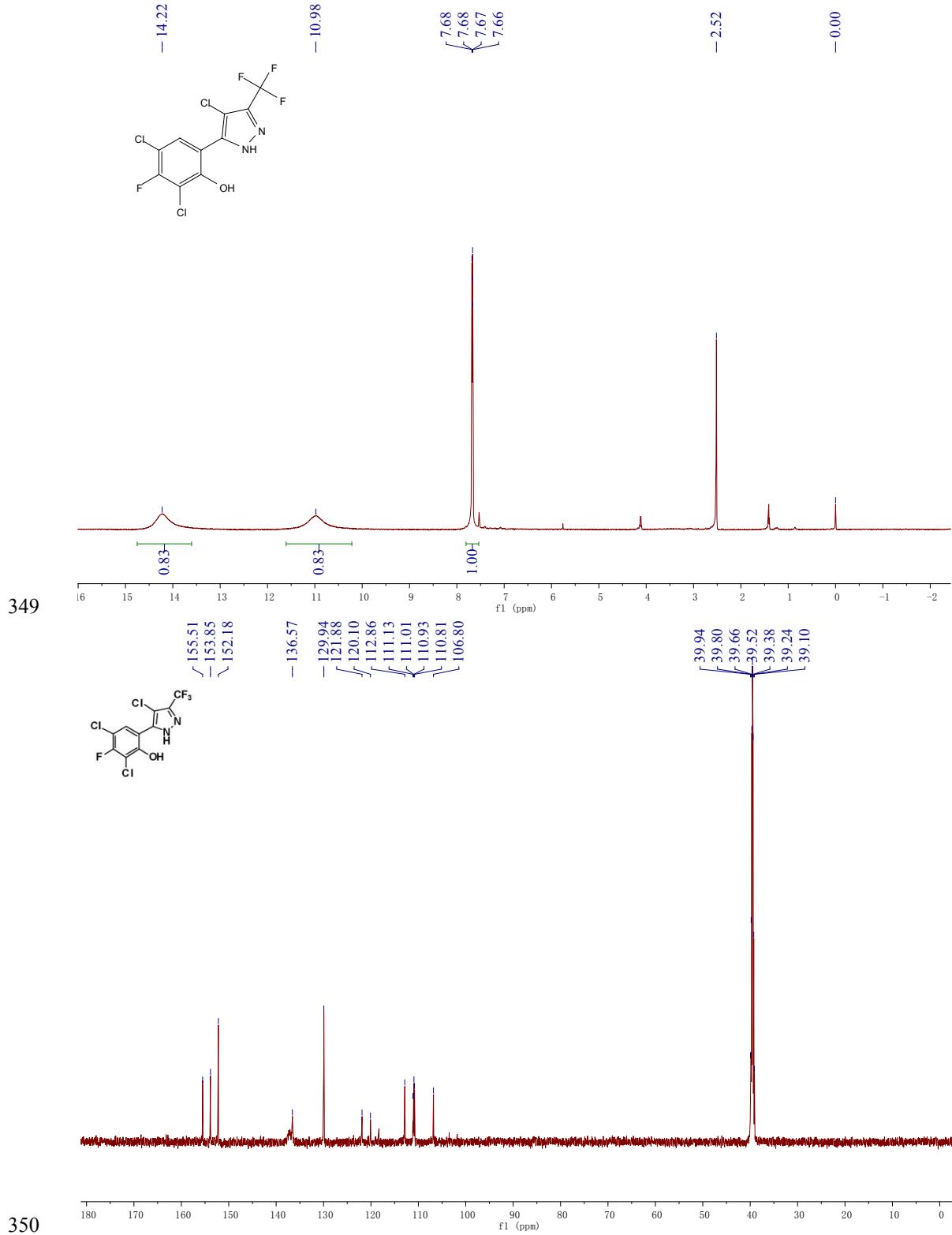


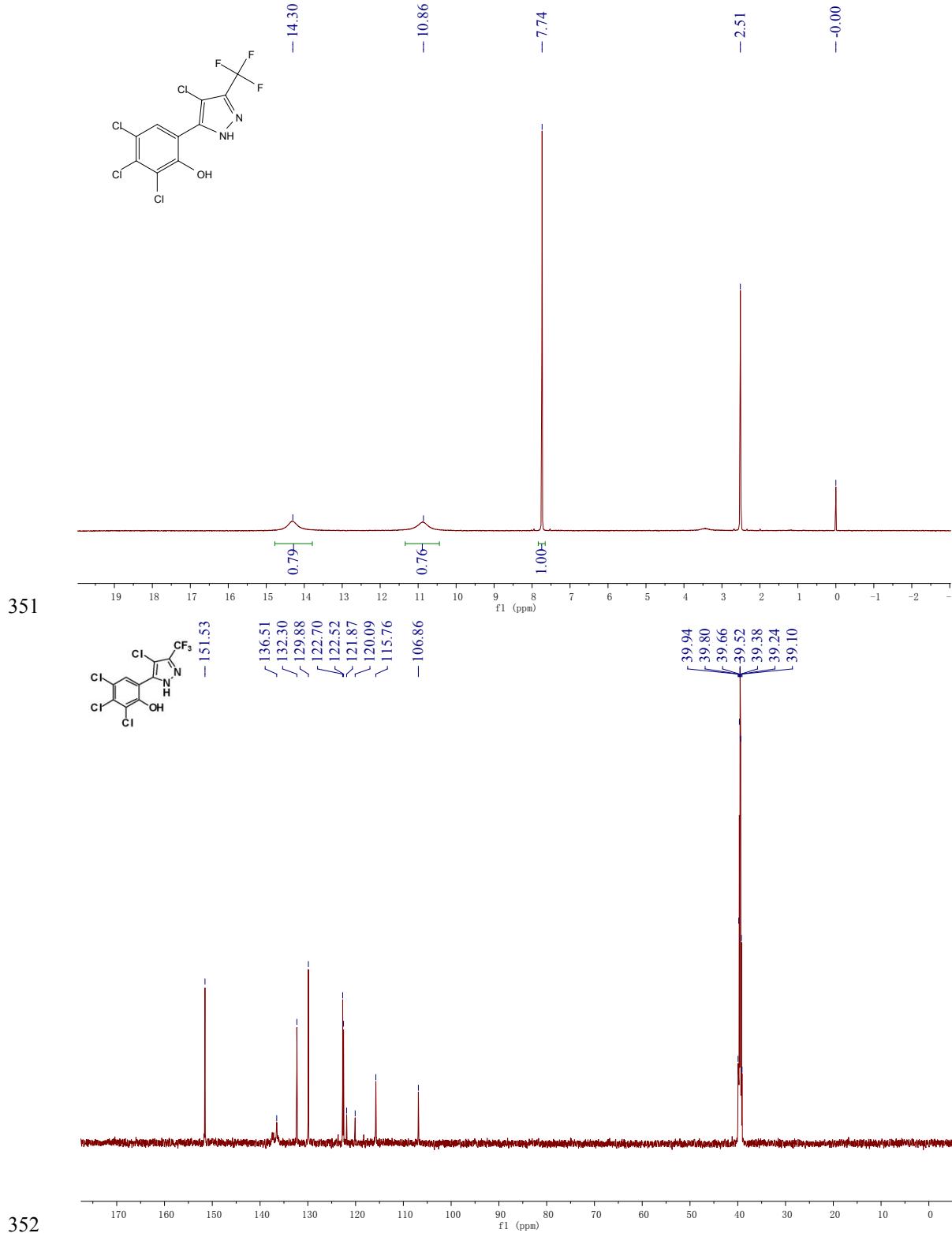


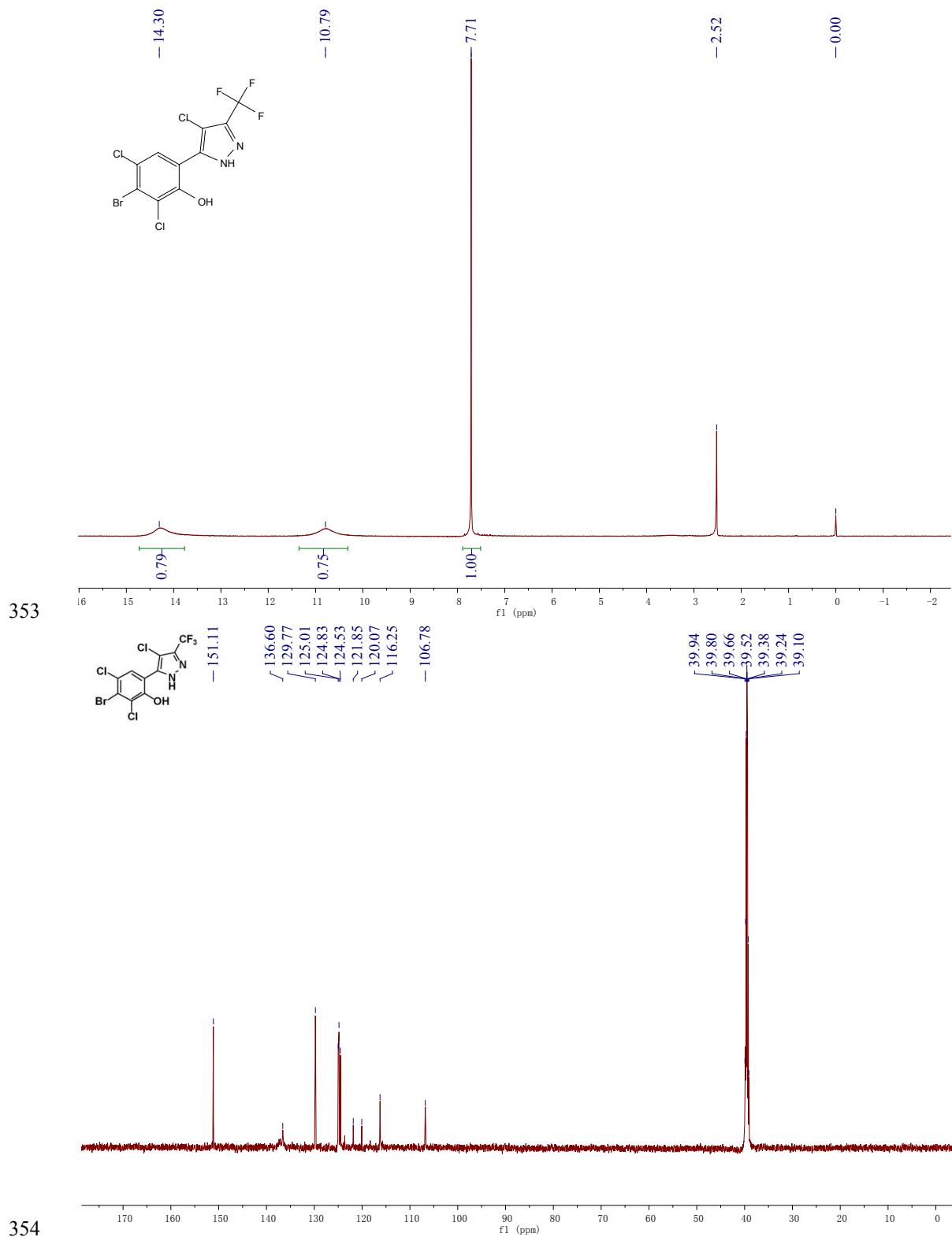


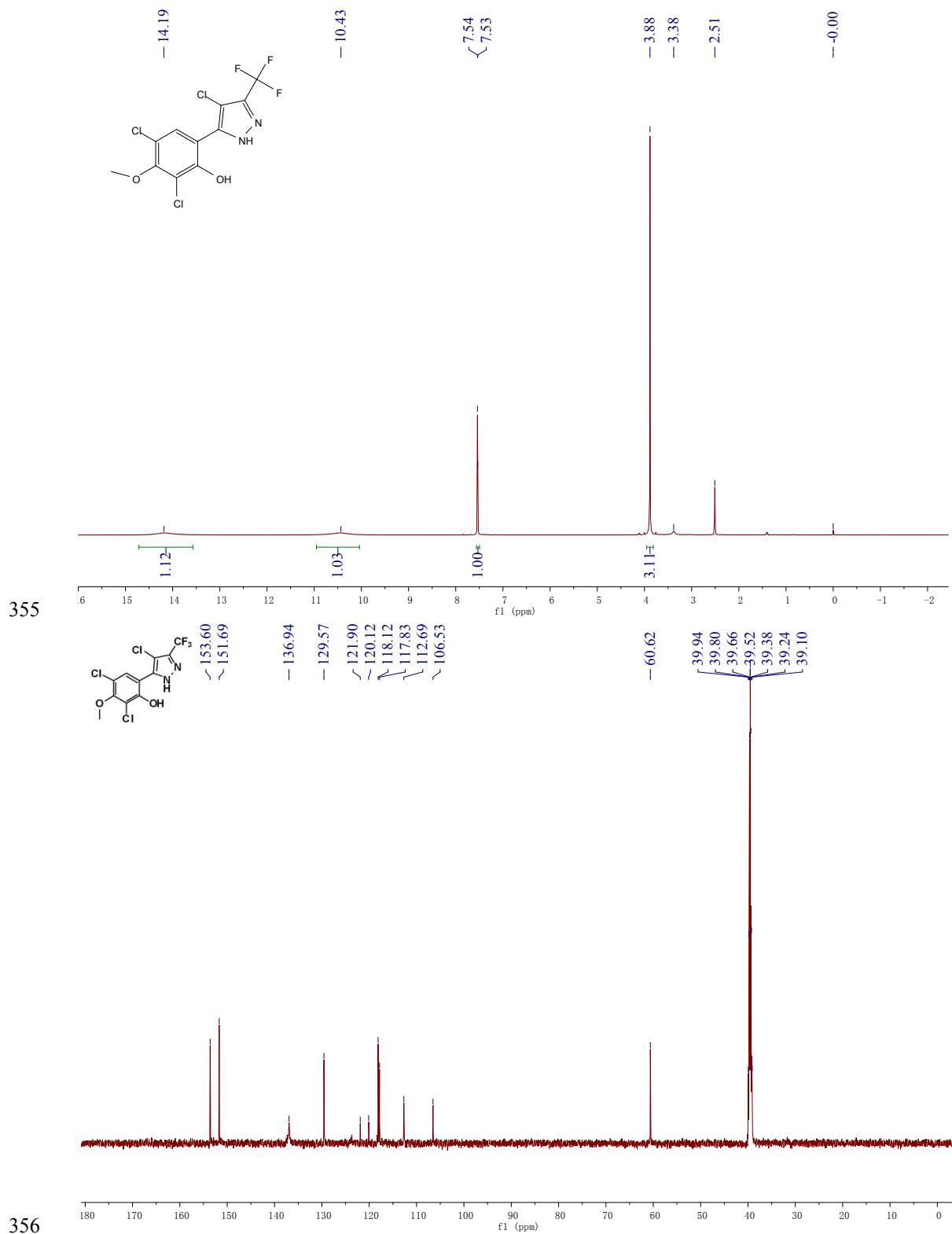


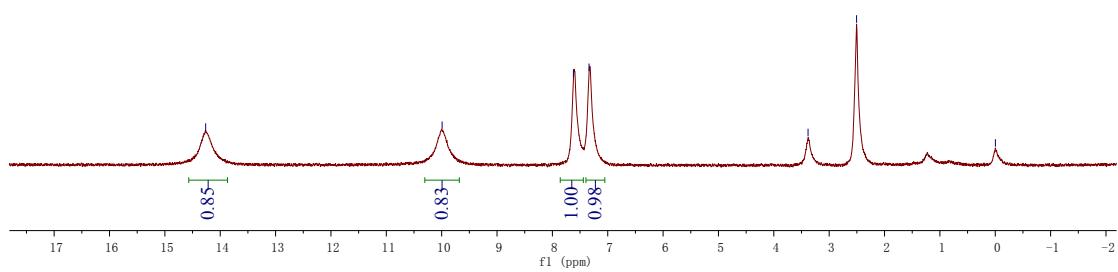
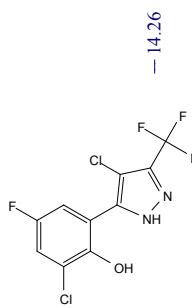




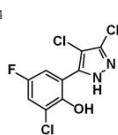




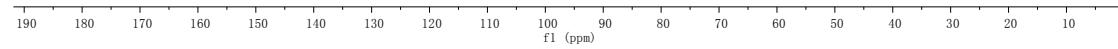


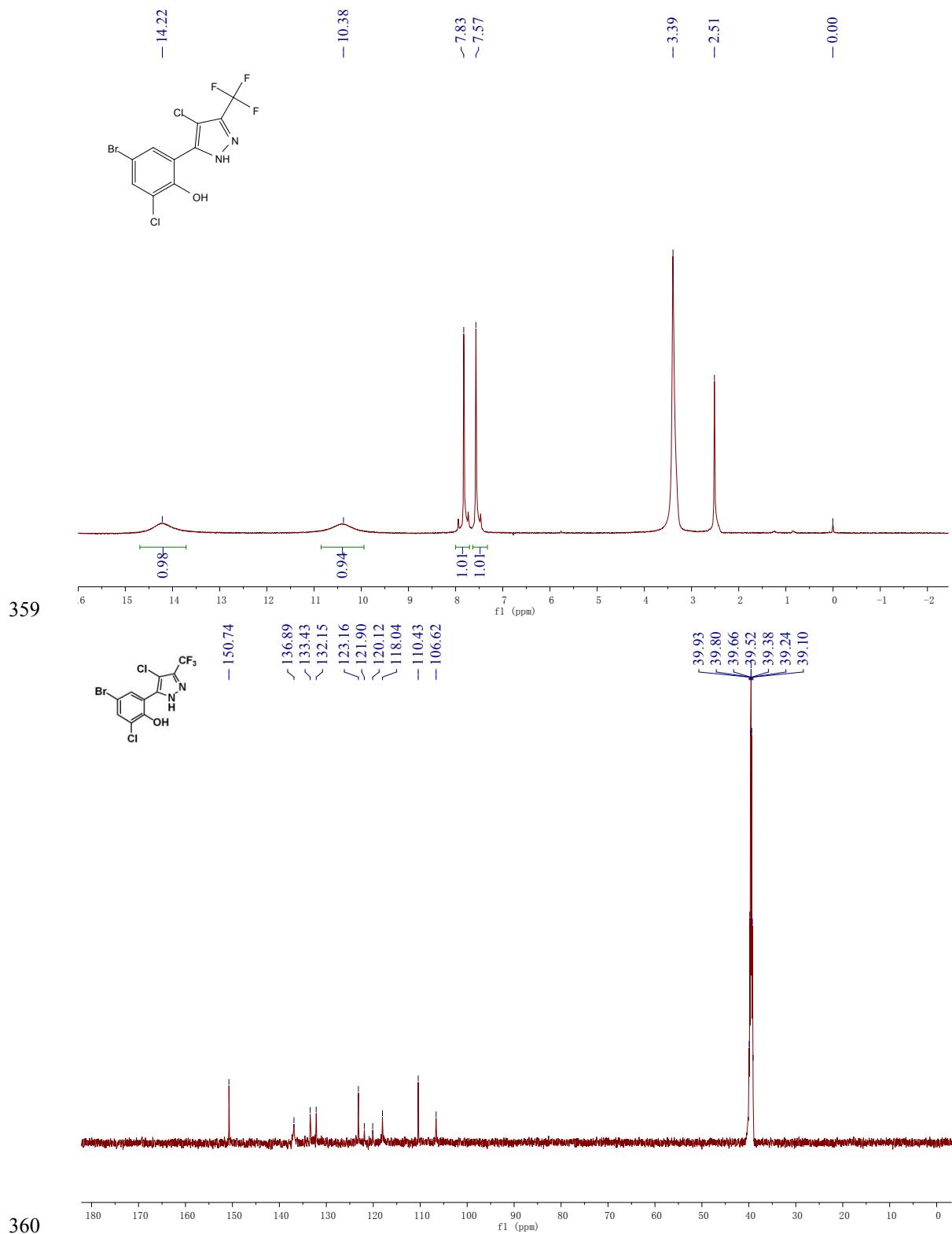


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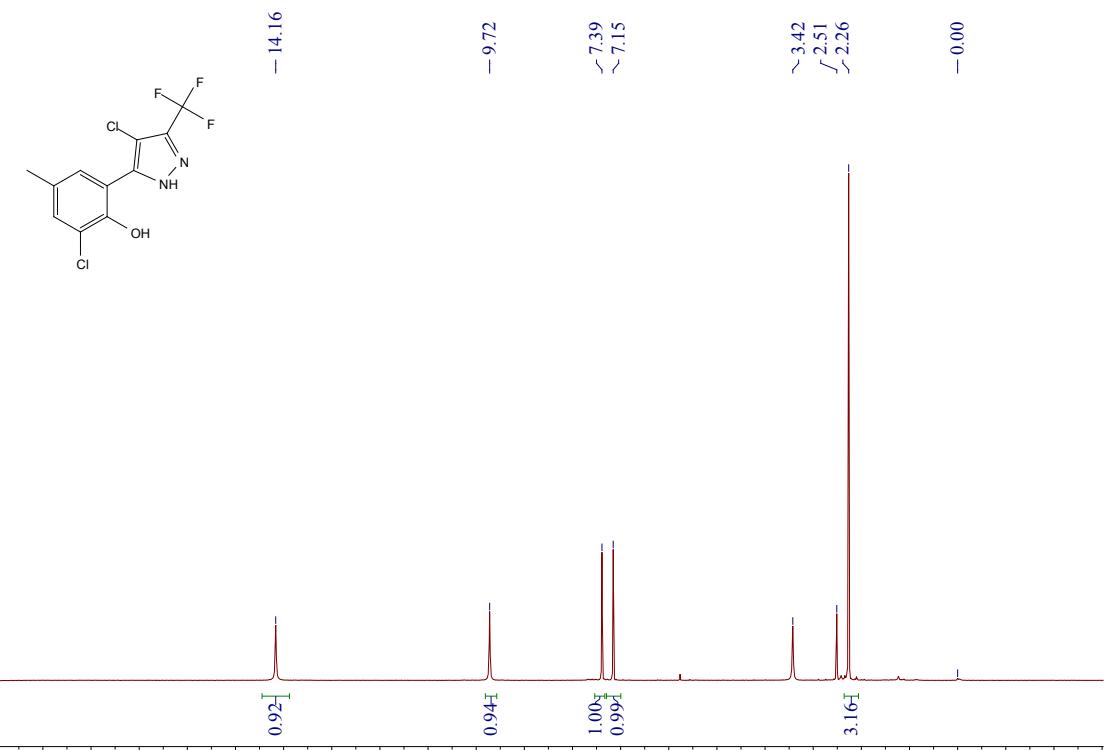


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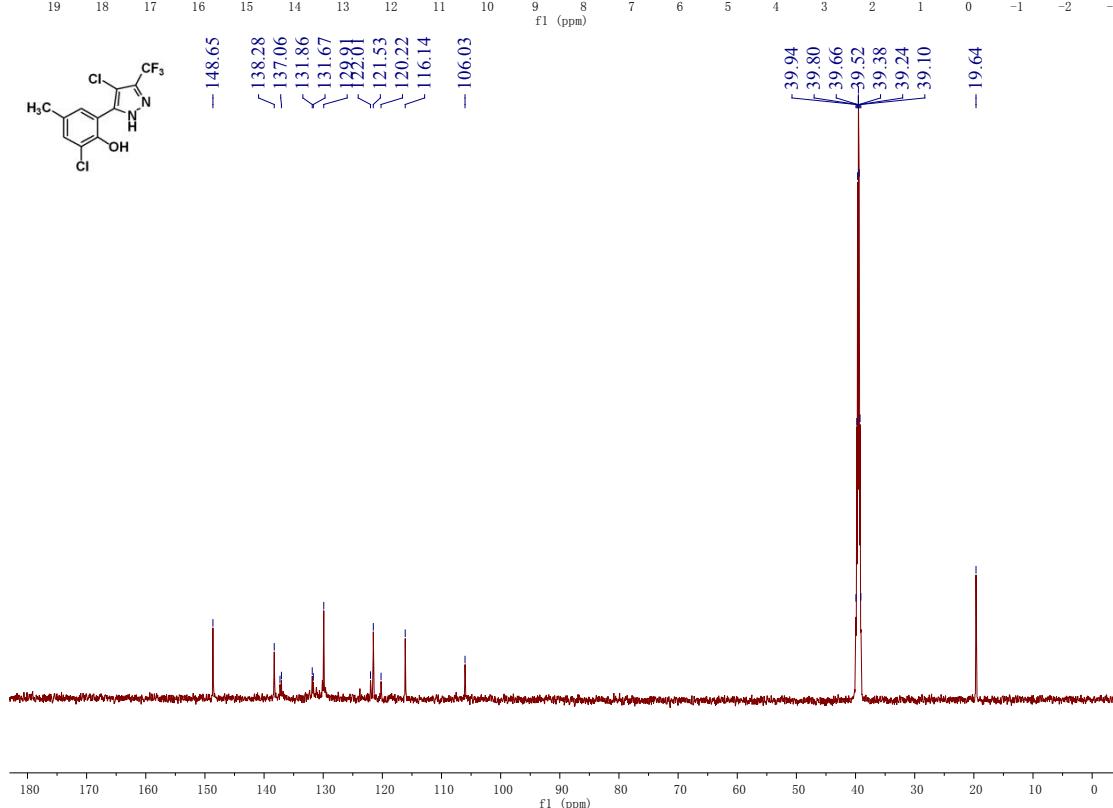


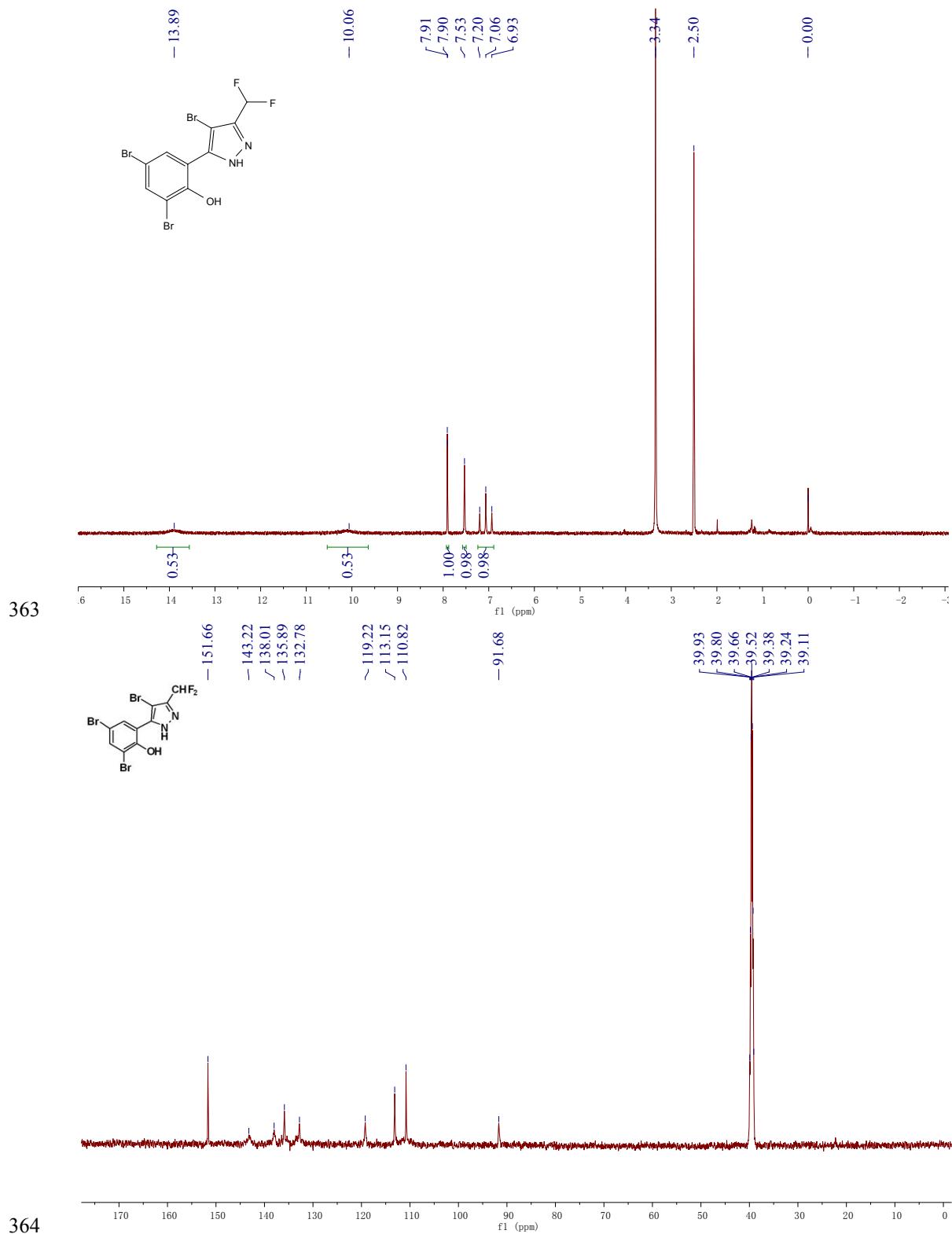


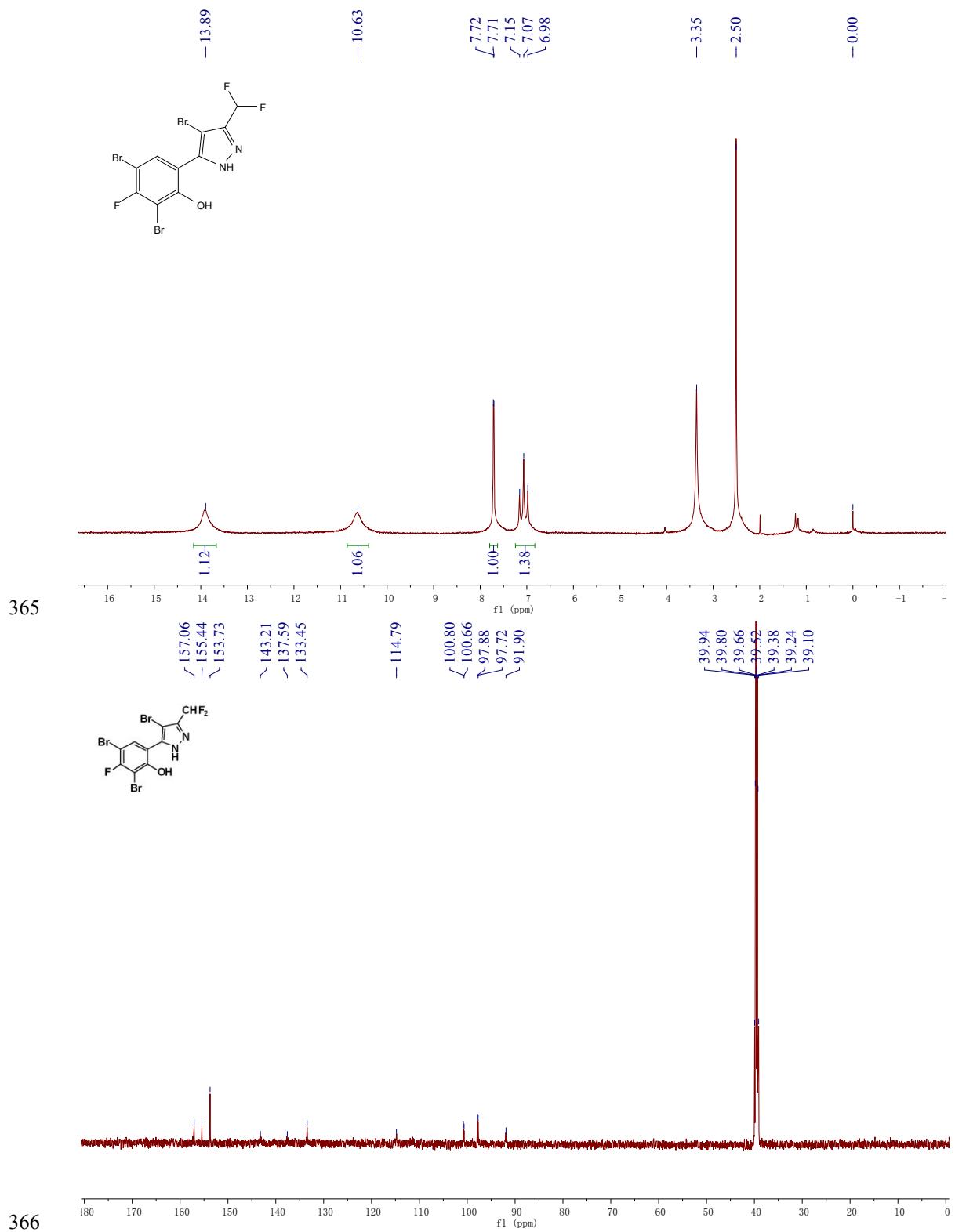
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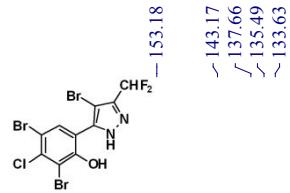
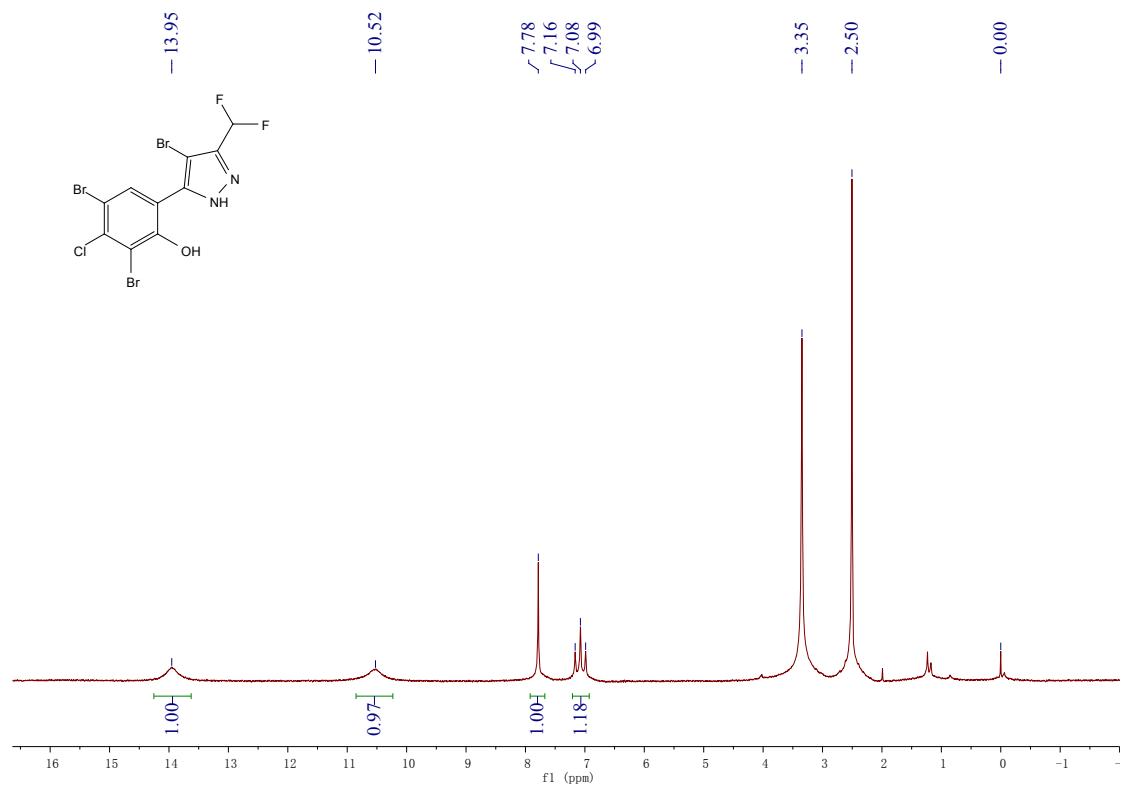
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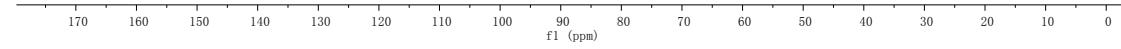


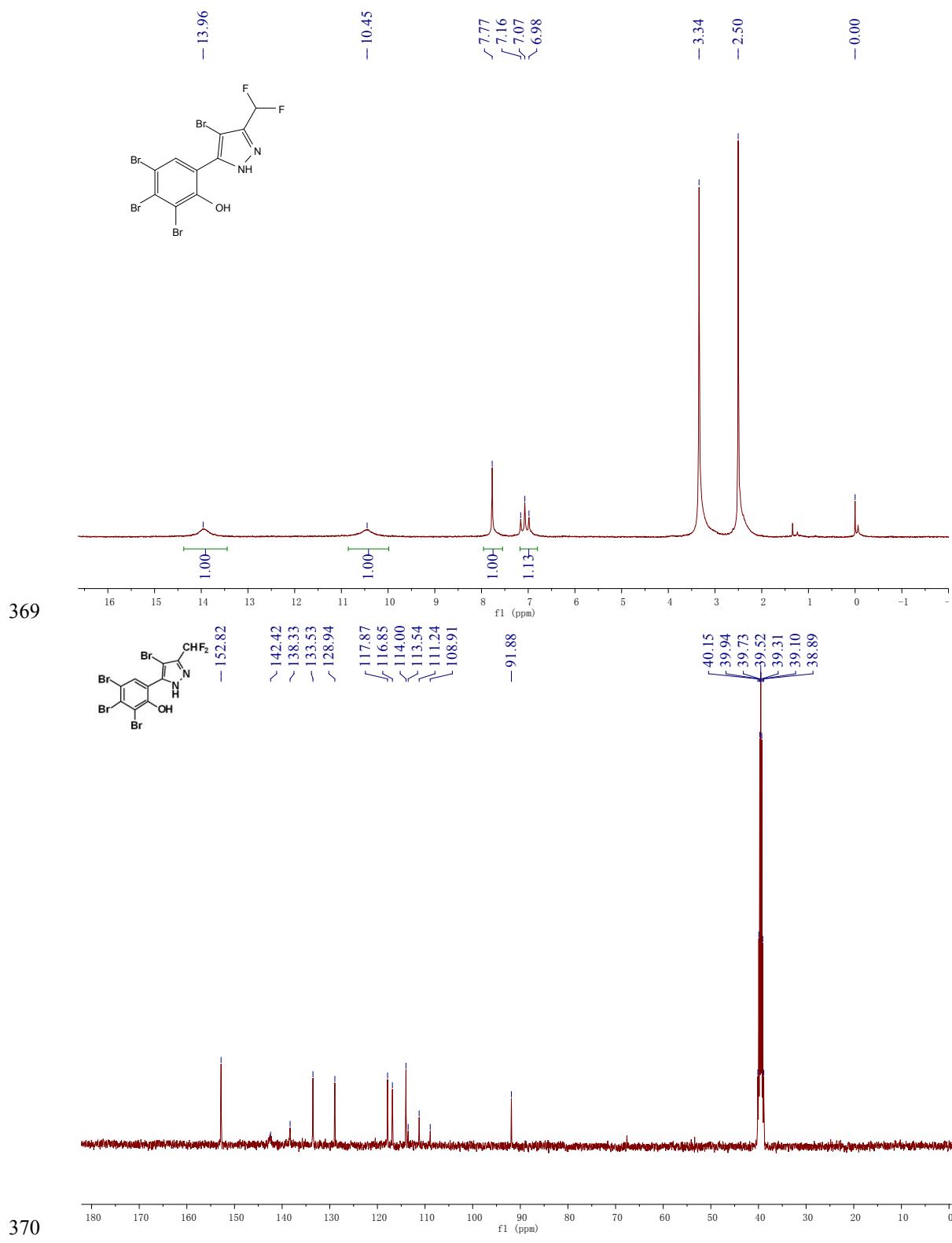


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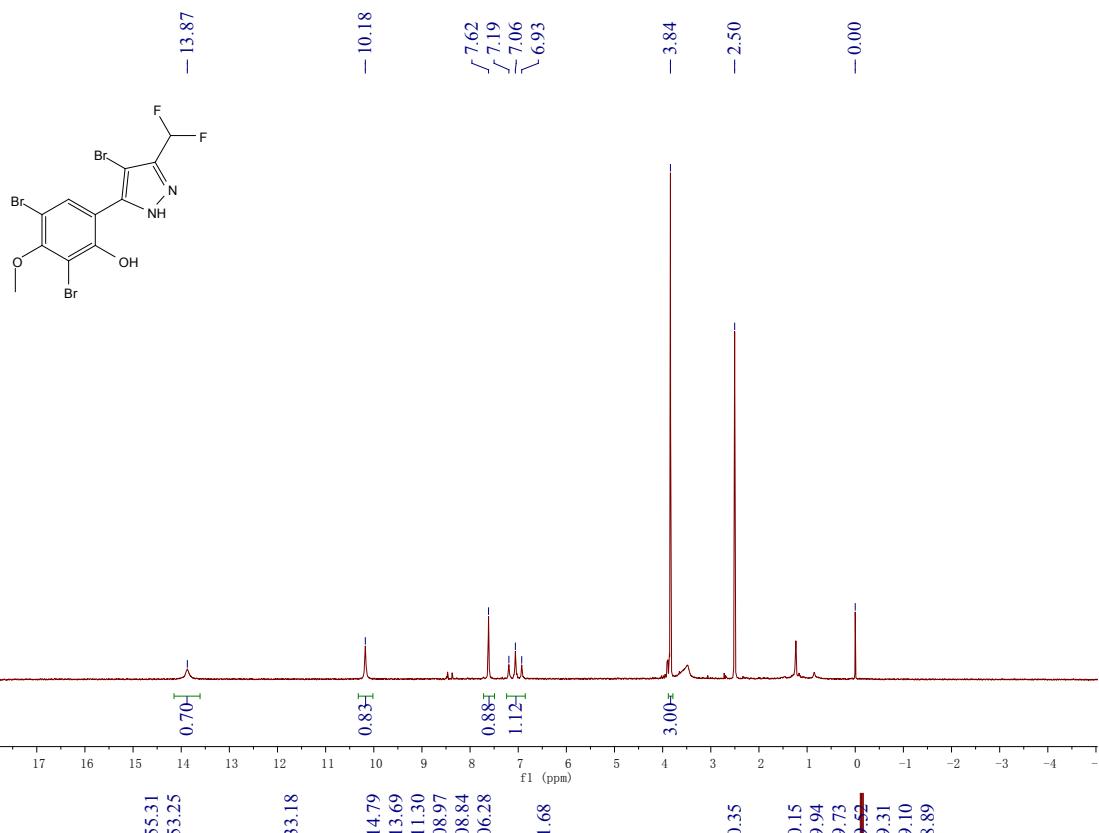


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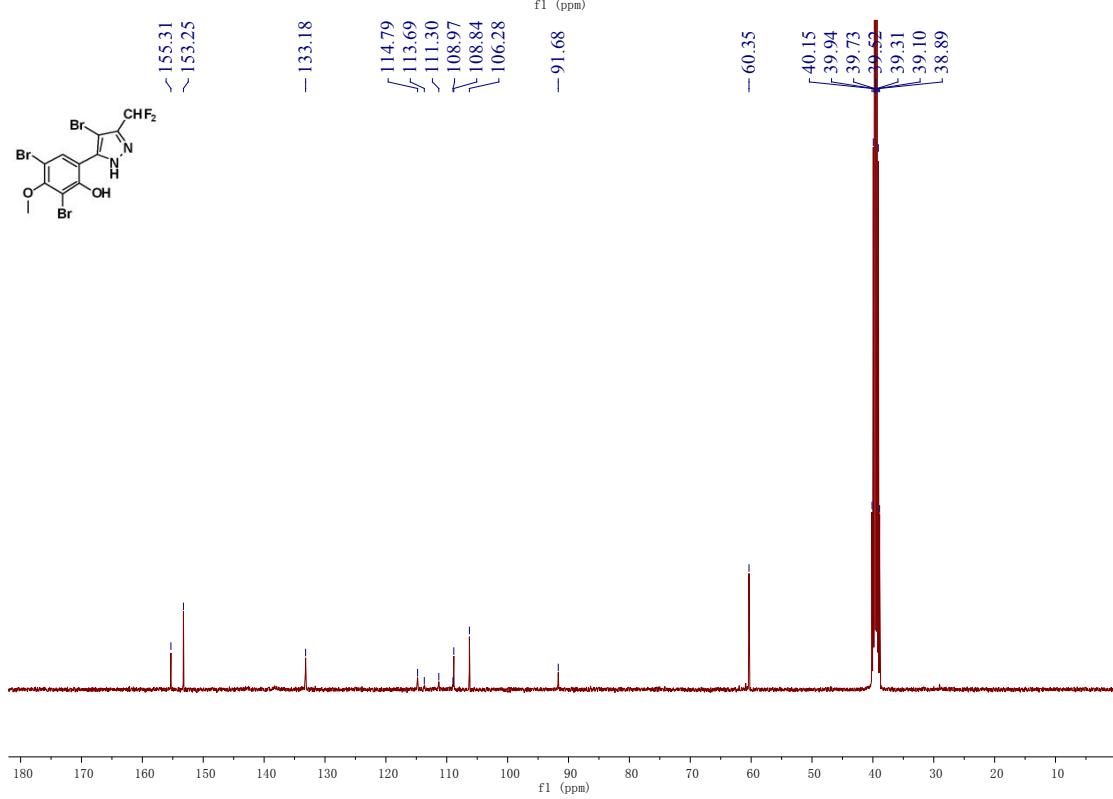


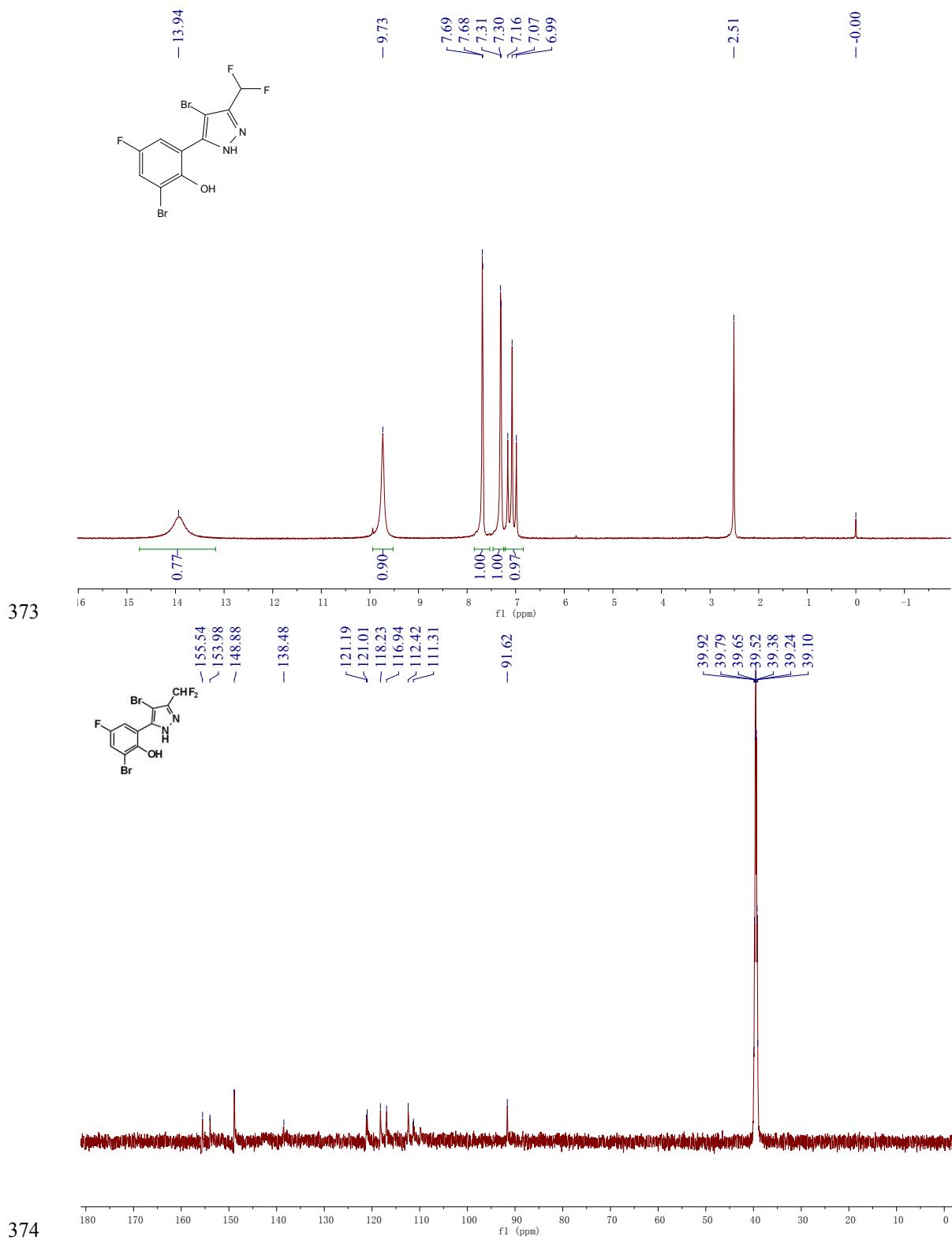


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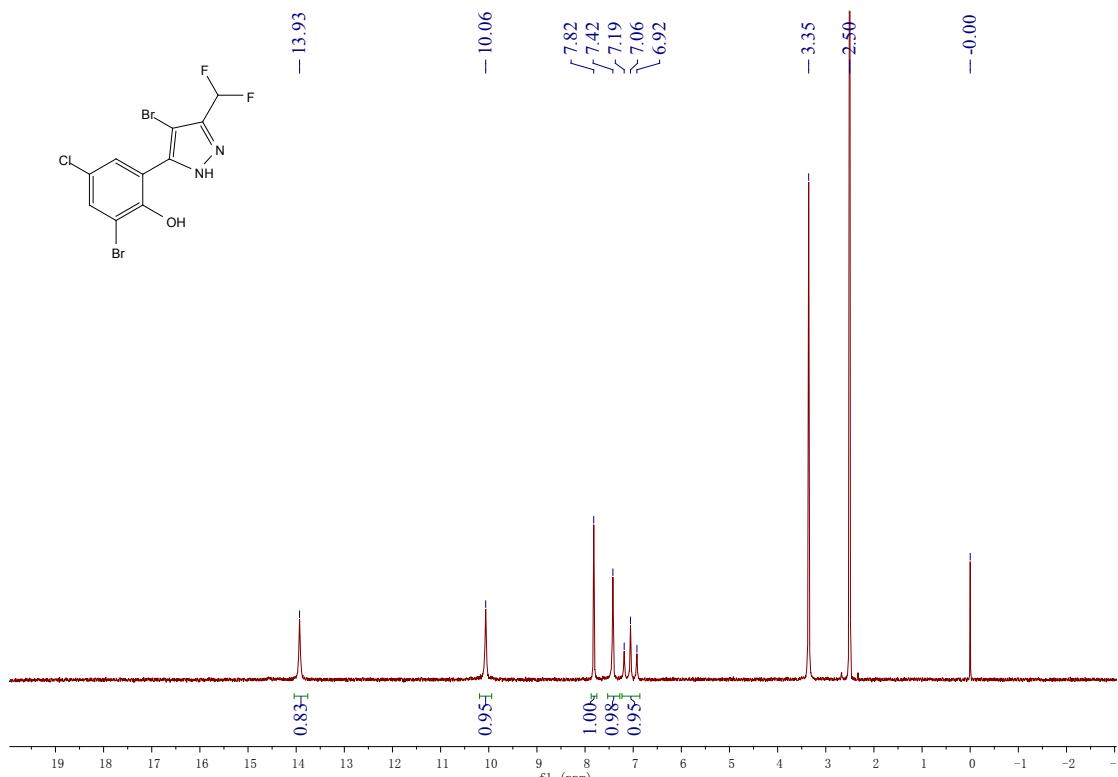


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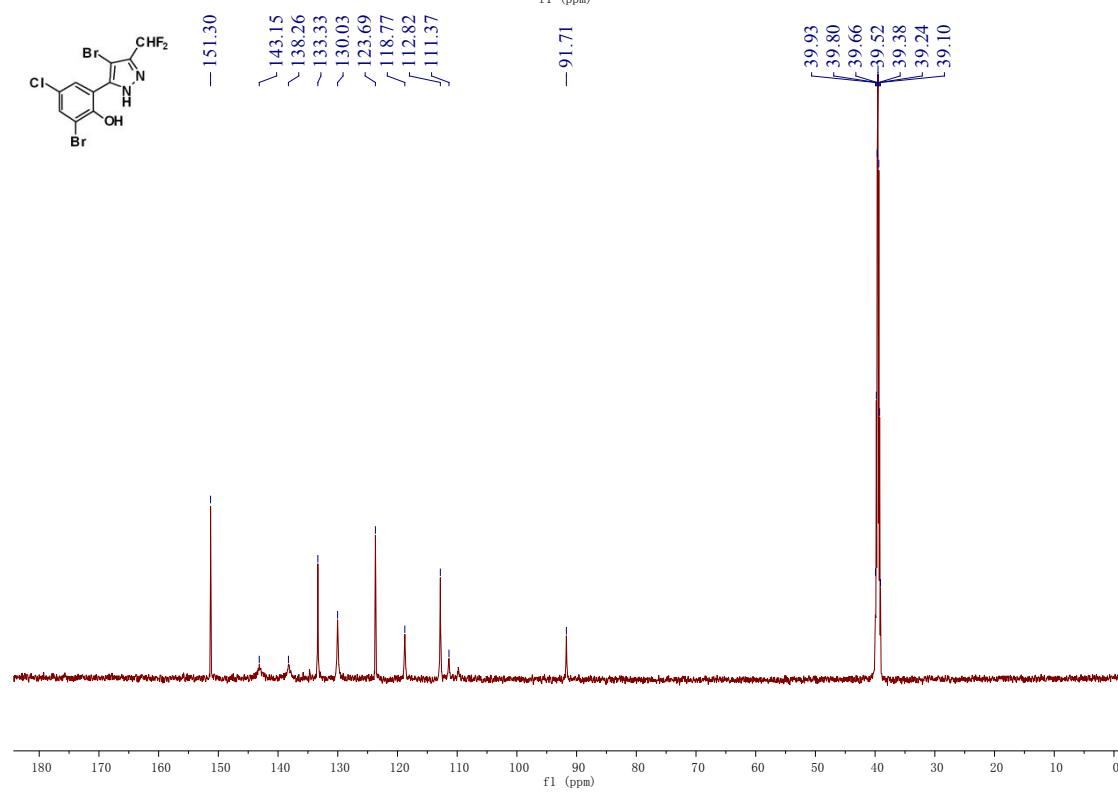


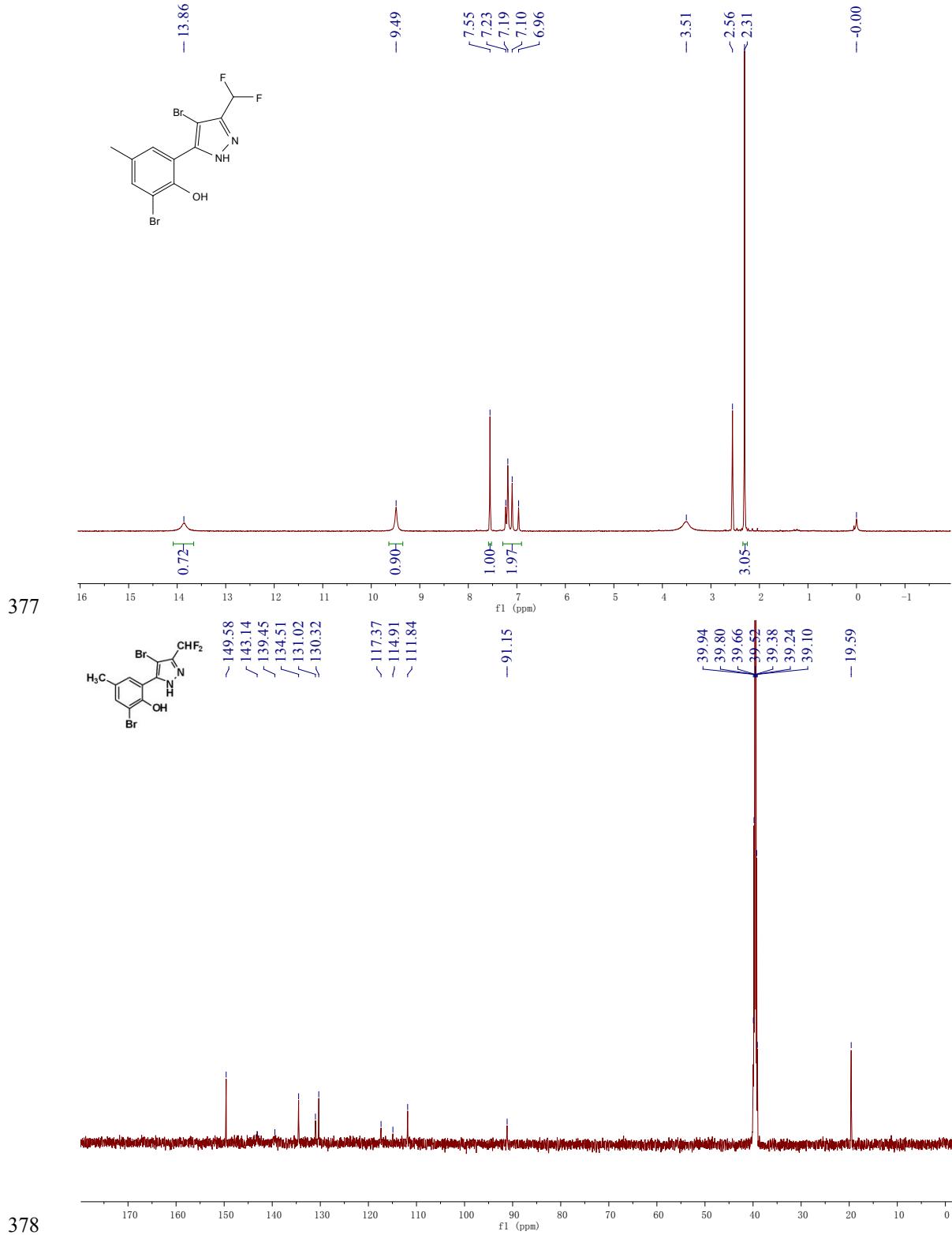


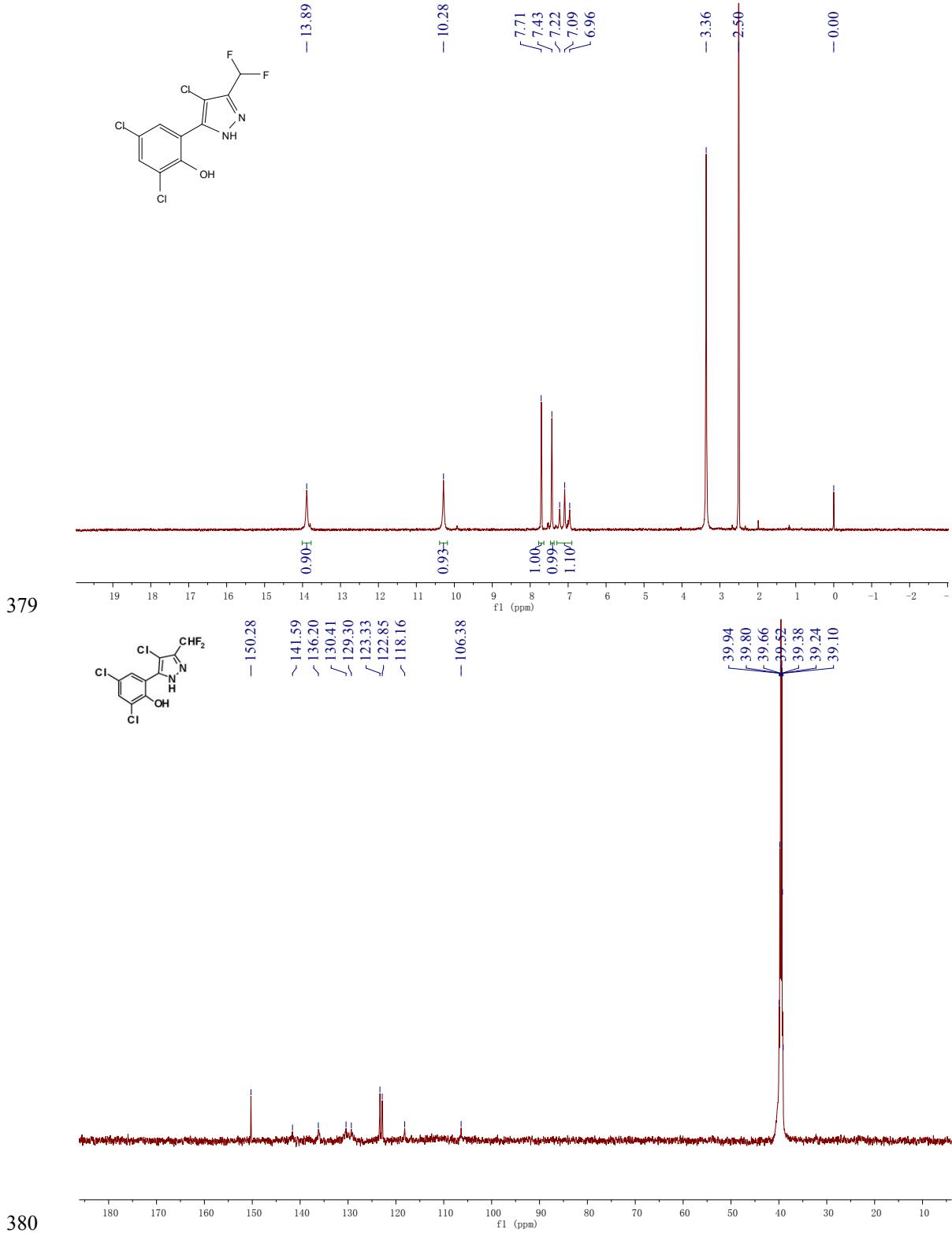
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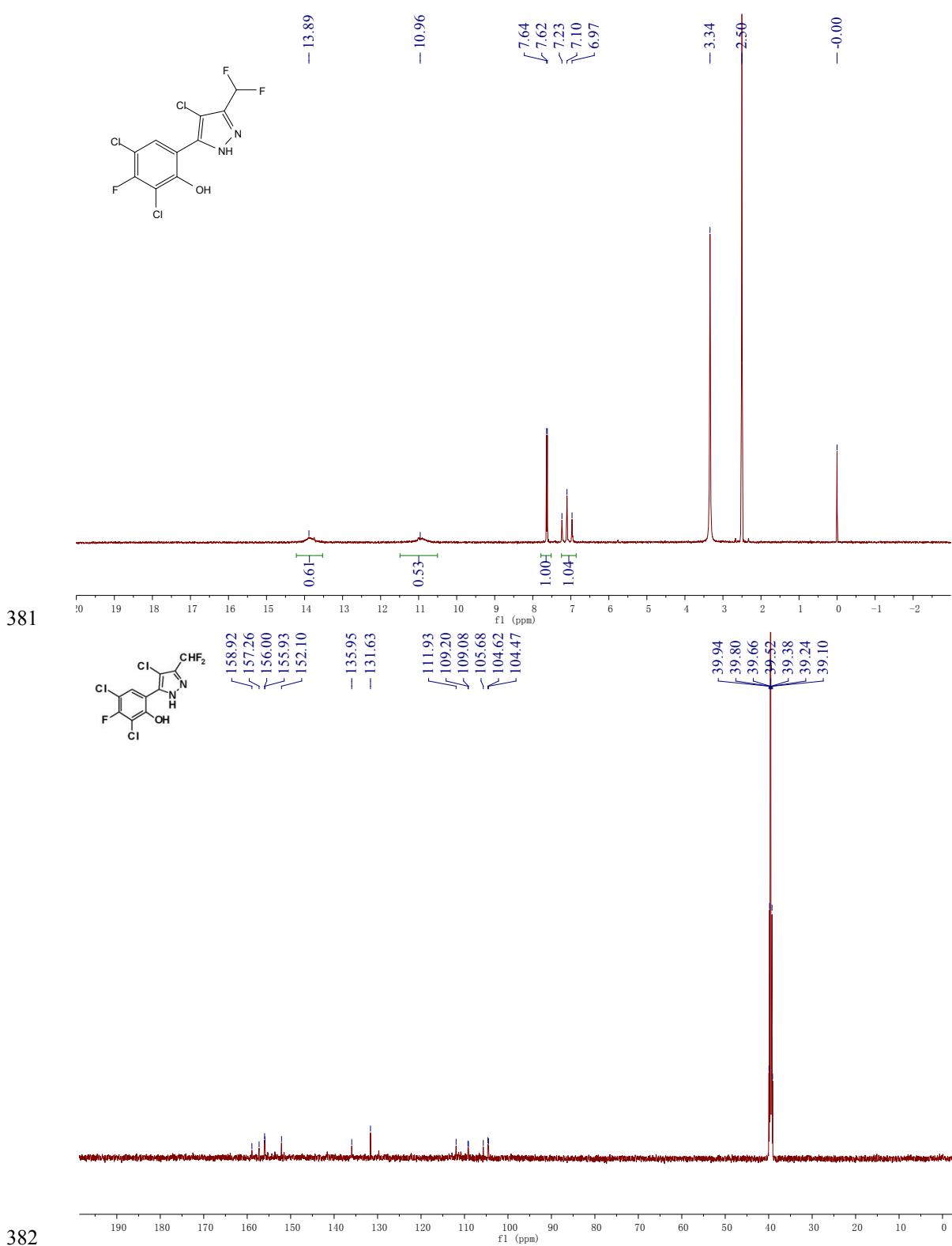


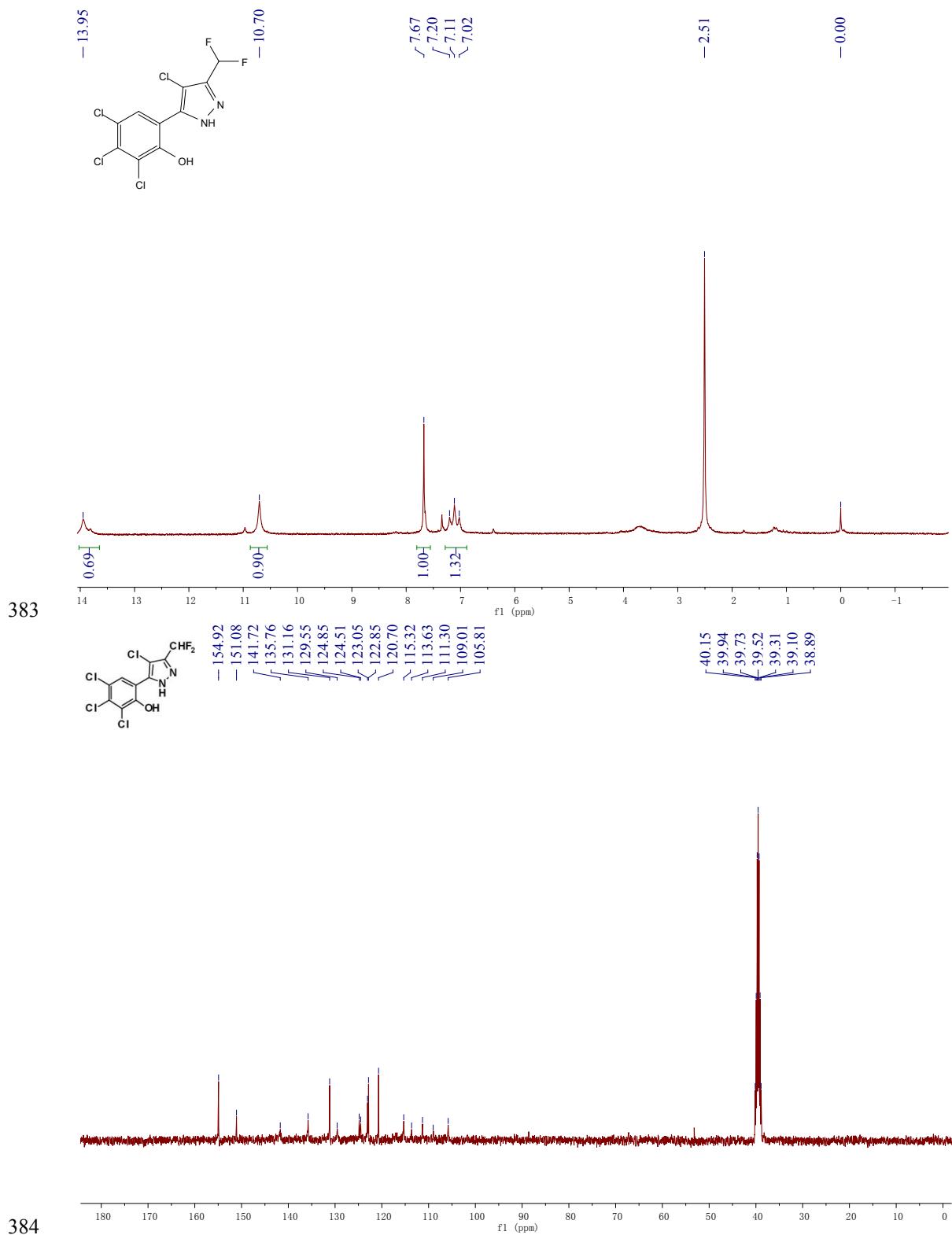
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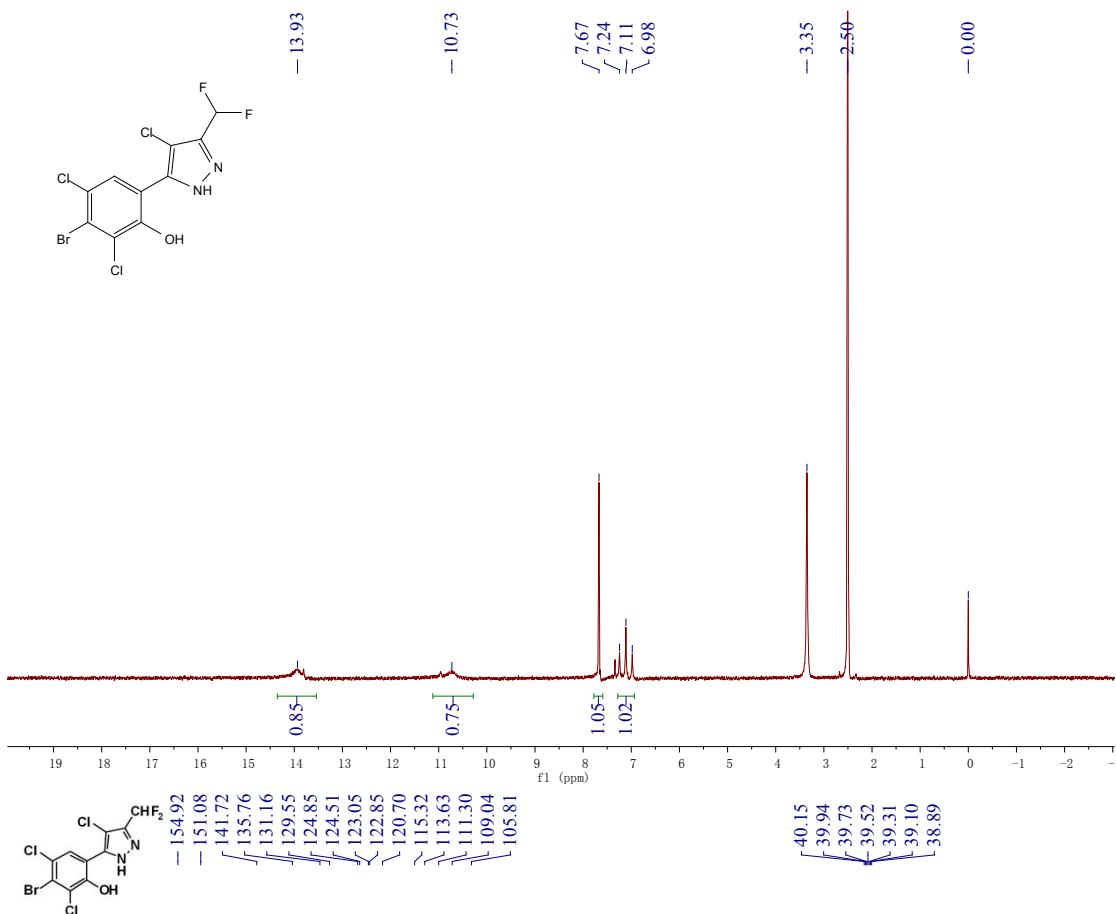




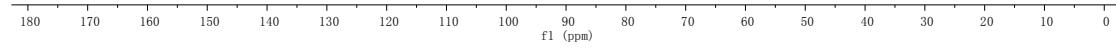




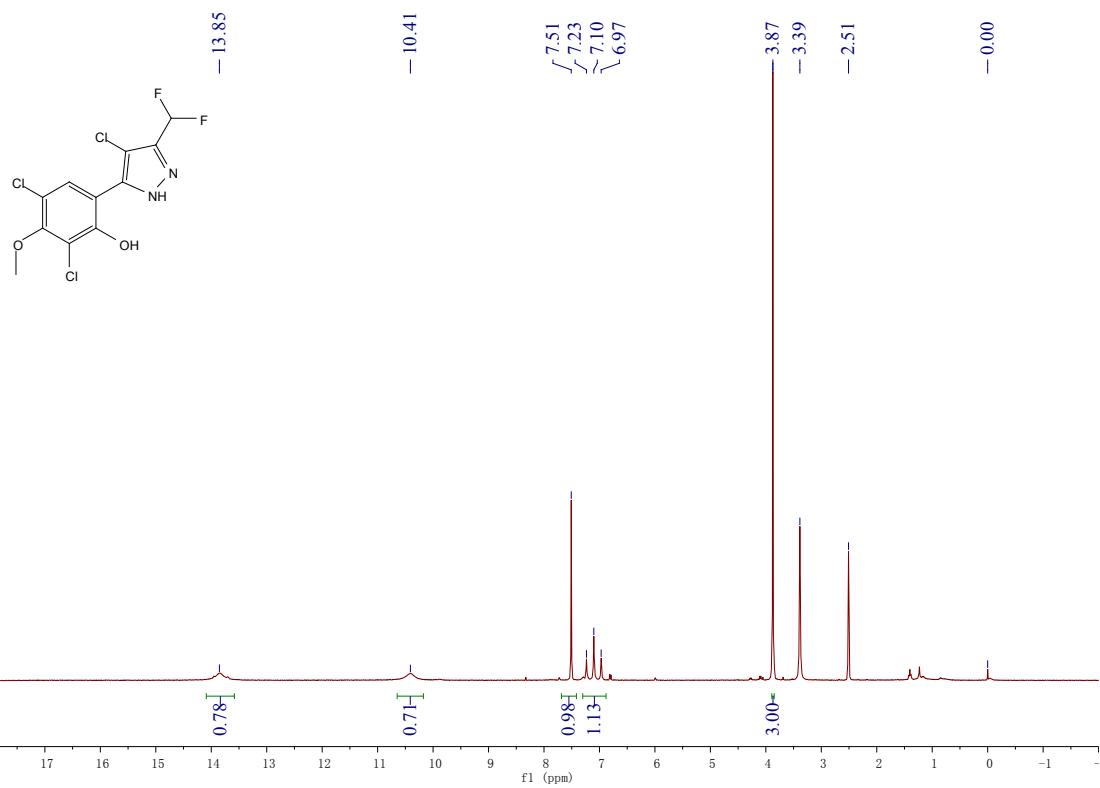
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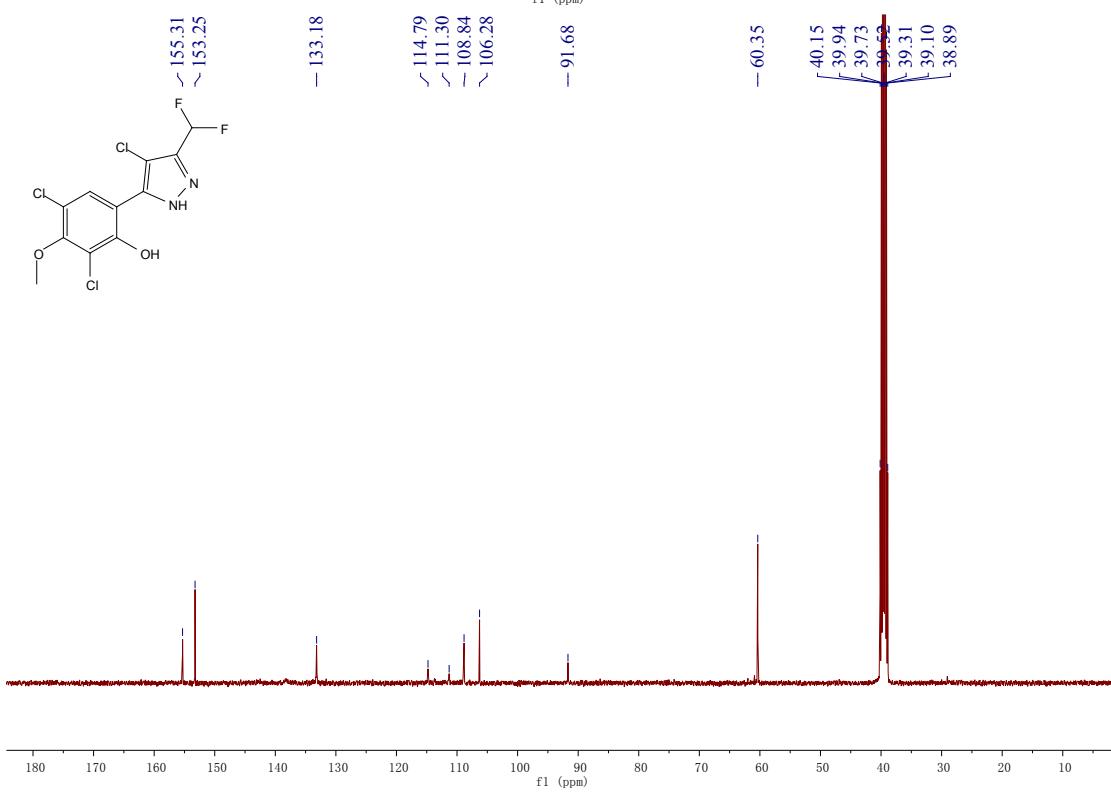
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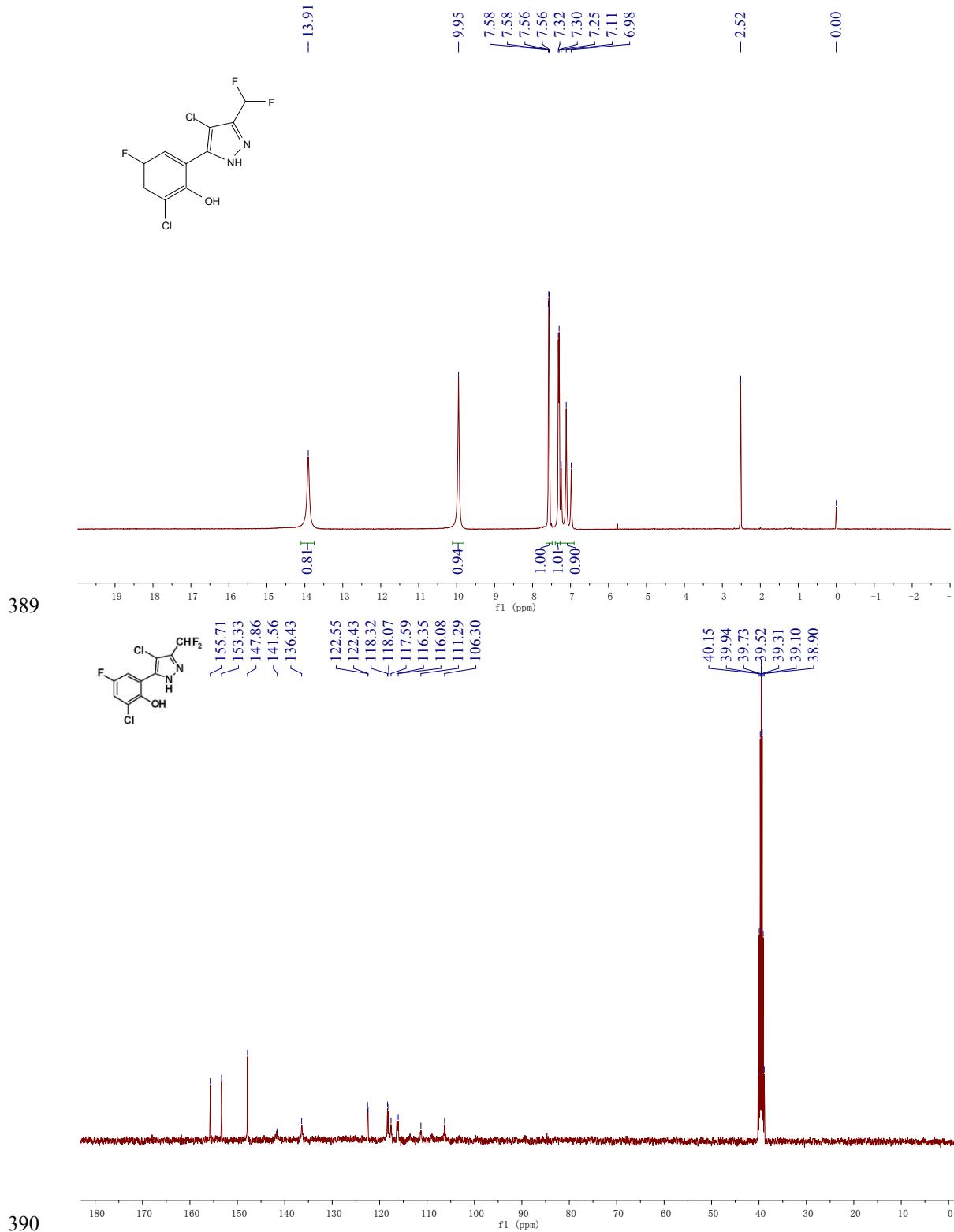


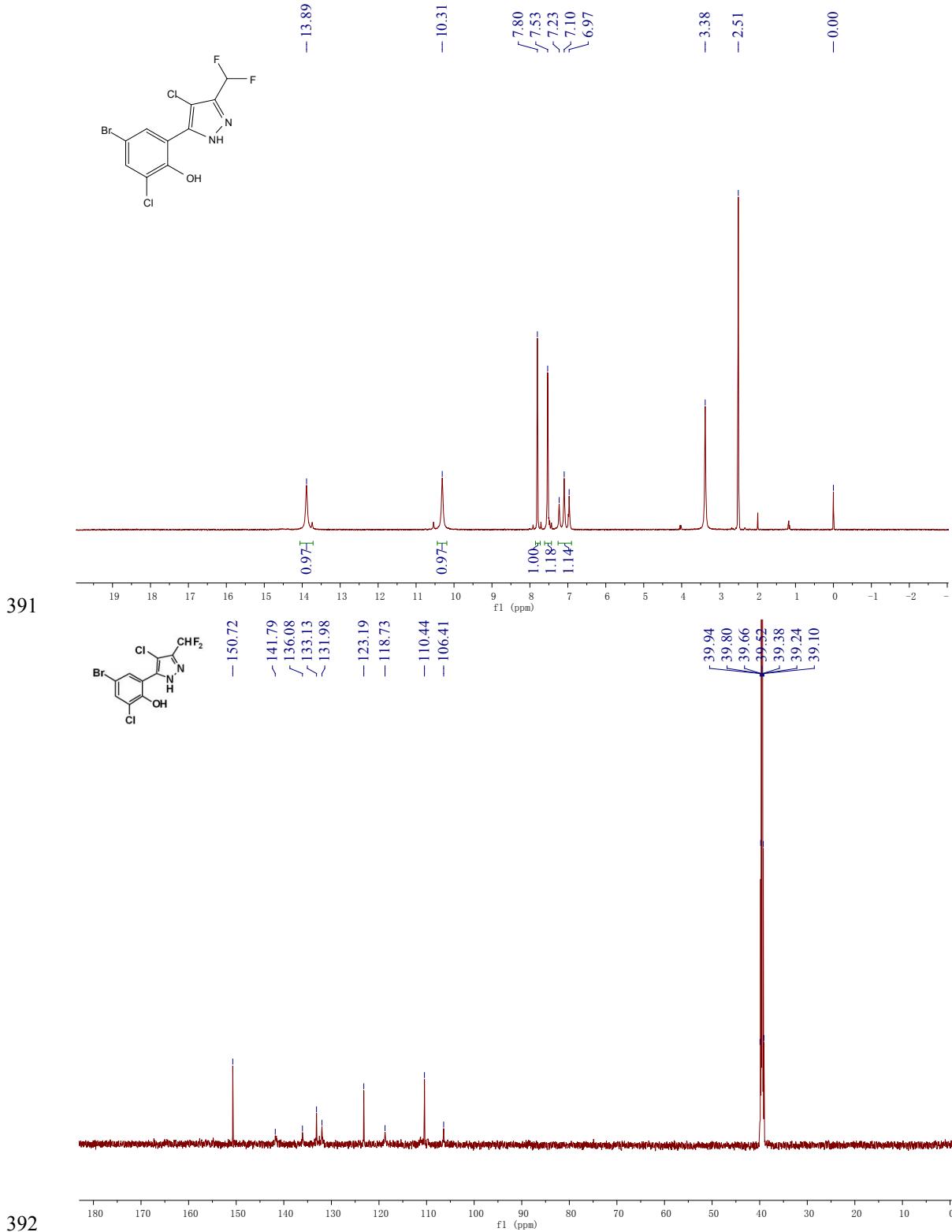
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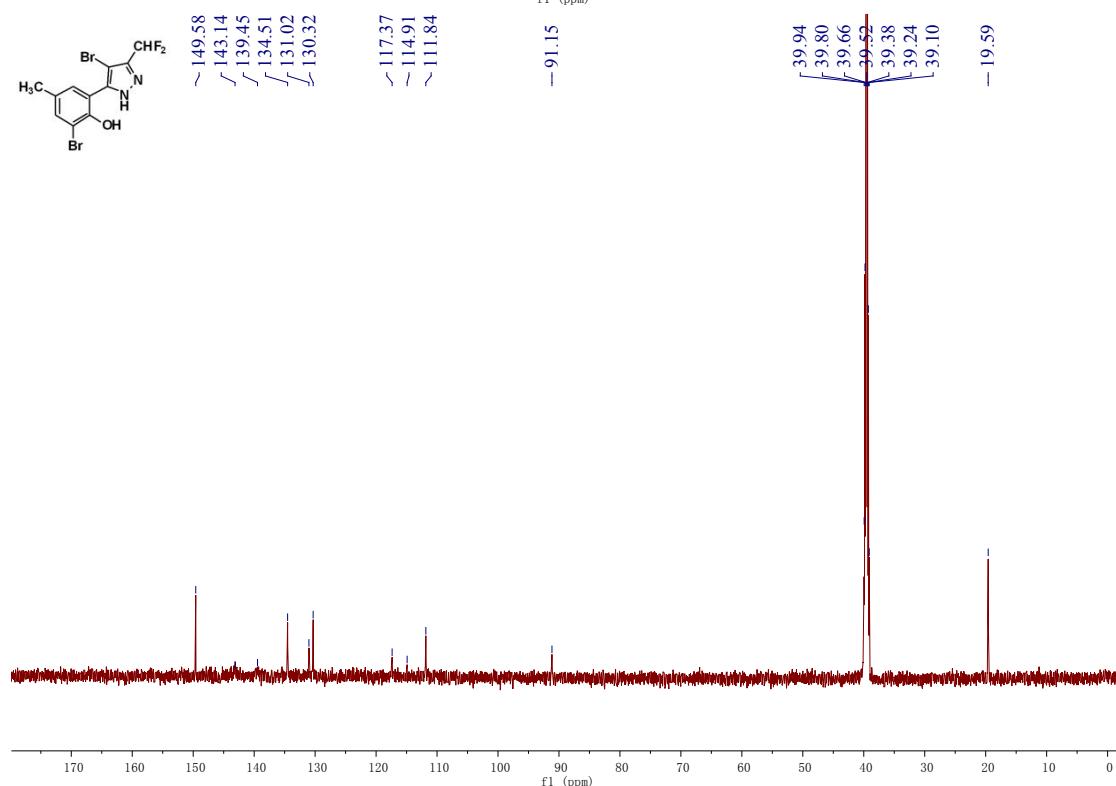
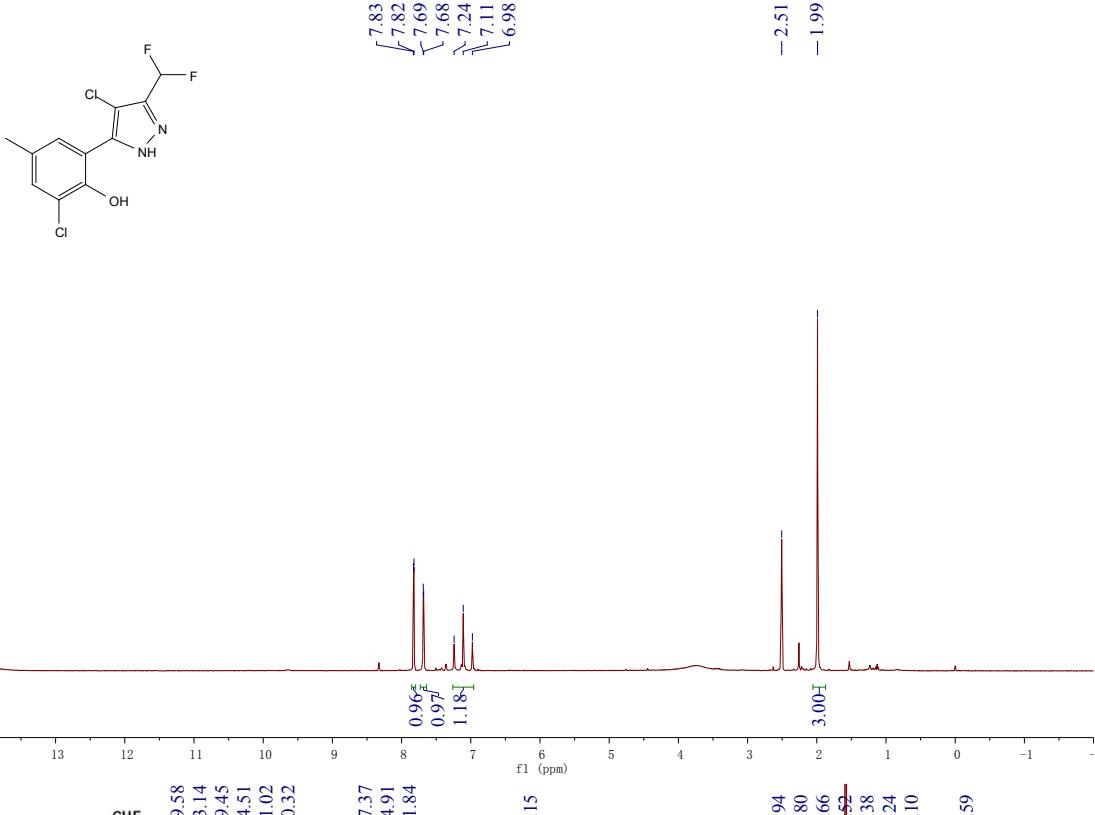


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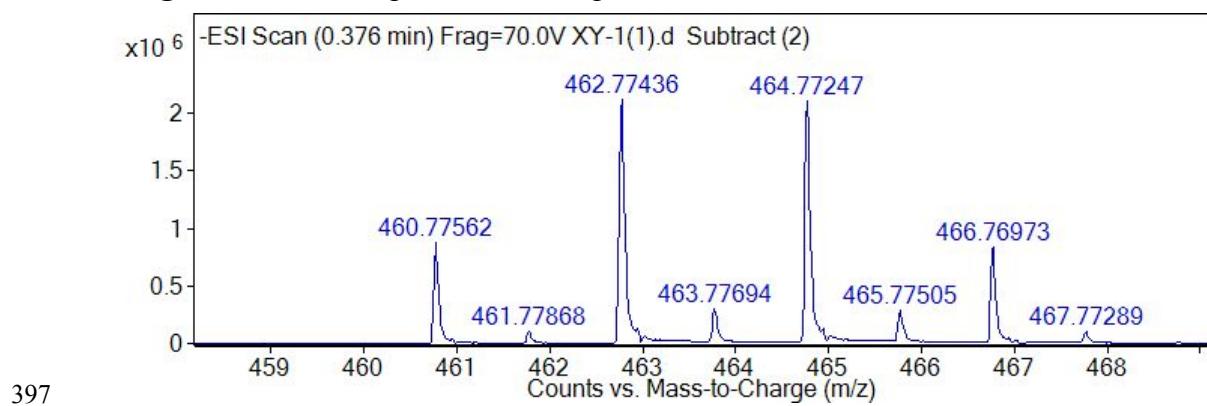








396 **7. Figure S1.** HRMS spectrum of compound **5a**



399 **8. Figure S2.** HRMS spectrum of compound **6b**

