Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry

One-pot syntheses of novel pyrazole-containing bisphosphonate esters at room temperature

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Supporting Information

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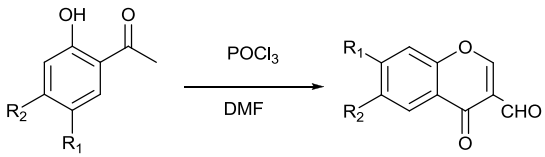
1. Experimental procedures

General information

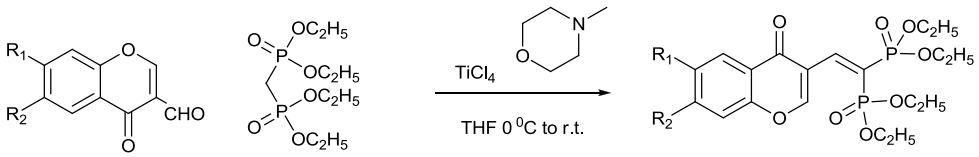
Unless otherwise noted, all solvents and other reagents are commercially available and used without further purification. ^{1}H, ^{13}C and ^{31}P NMR spectra were recorded on Varian Mercury-300/400 and Varian Mercury-400/500 spectrometers. MS and HRMS spectra were performed on a Finnigan MAT 95 spectrometer. Melting points were measured by Büchi 510 melting point apparatus without further corrected.

Preparation of the starting material substituted 3-formyl-4-chromenones



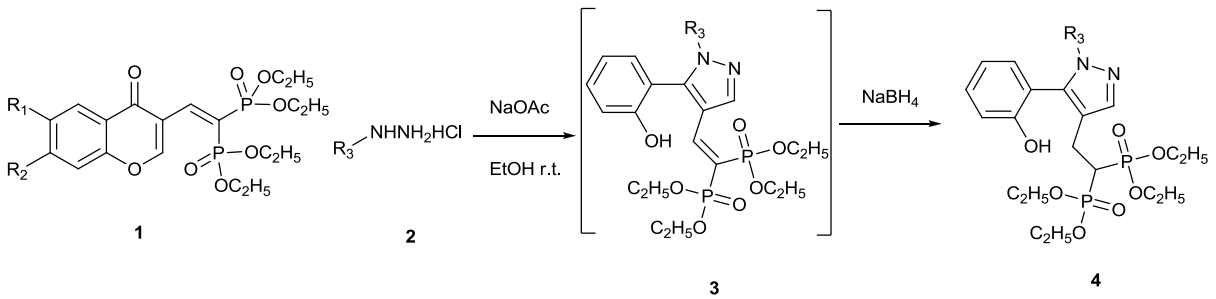
Dimethylformamide (6.0 mL) was cooled in ice-cold water and 2-hydroxy acetophenone (0.01 mmol) was added to this with vigorous stirring; phosphorus oxychloride (2.0 mL) was slowly added into the solution. The pink colour thick mass was kept overnight at room temperature. The mixture was then decomposed by cold water and extracted by EtOAc (3×100 mL). Concentrated under reduced pressure, the crude product was further purified by column chromatography (PE: EtOAc 10:1).

General procedure for the syntheses of compounds 1a-1d.



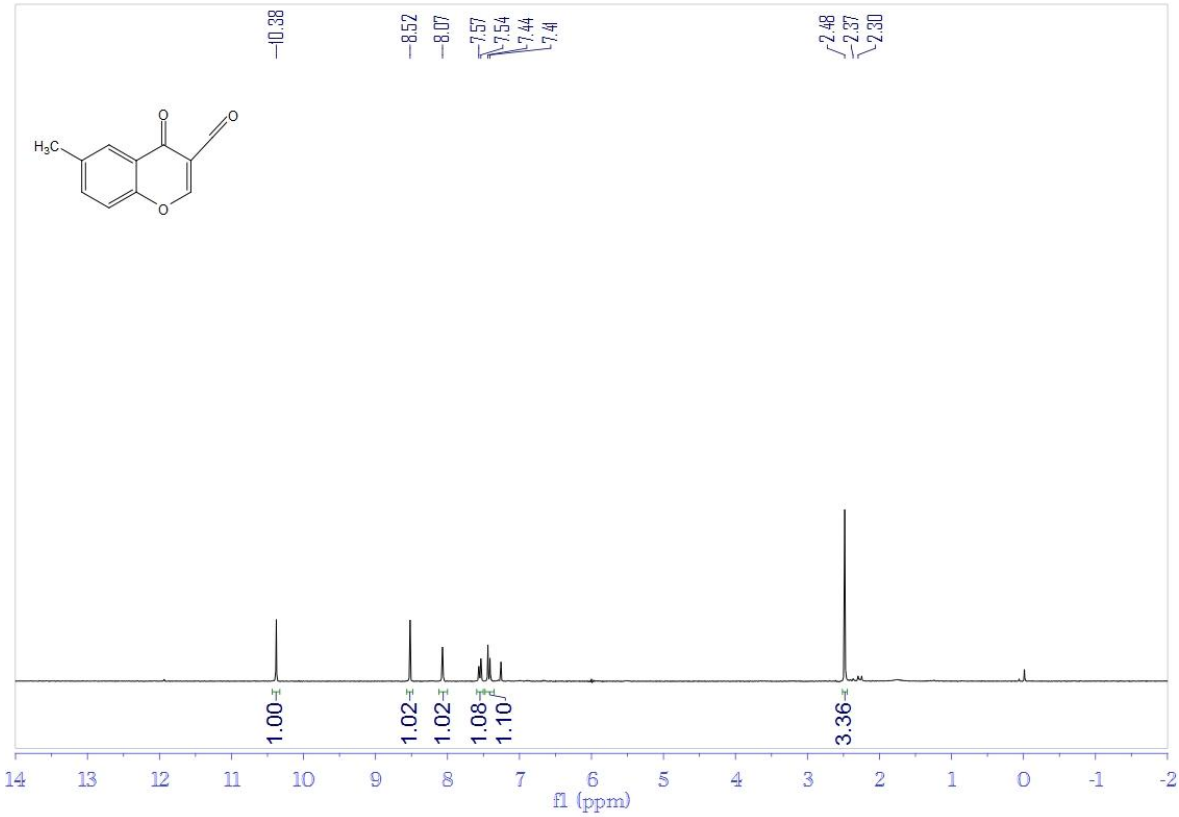
Firstly, 100 mL of dry THF was placed in a 250 mL flask and cooled to 0 ℃ under nitrogen and 3-formyl chromone (4 mmol), Titanium tetrachloride (1.97g, 10.4 mmol), tetraethyl methylenebisphosphonate (1.16g, 4 mmol) and N-methylmorpholine (2.1g, 20.8mmol) were added successively. Then the mixture was partitioned between EtOAc (100 mL) and H_2O and extracted by EtOAc (100 mL) twice after stiring for 3-4 h at room temperature. Combined the organic layer , washed with aqueous $NaHCO_3$ to neutral, dried over anhydrous Na_2SO_4, and evaporated to dryness under reduced pressure, the crude product was further purified by column chromatography (CH_2Cl_2: MeOH 100:0 - 40:1).

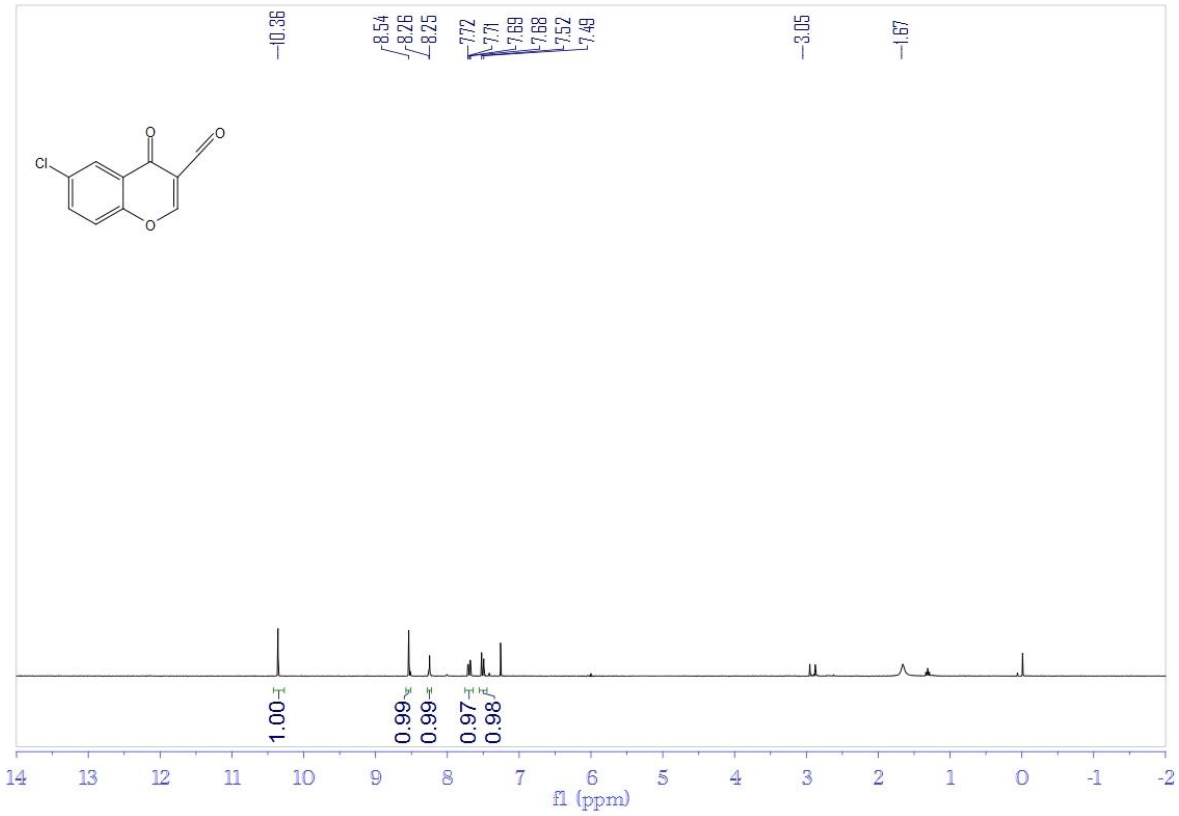
General procedure for the syntheses of compounds 4a-4v.

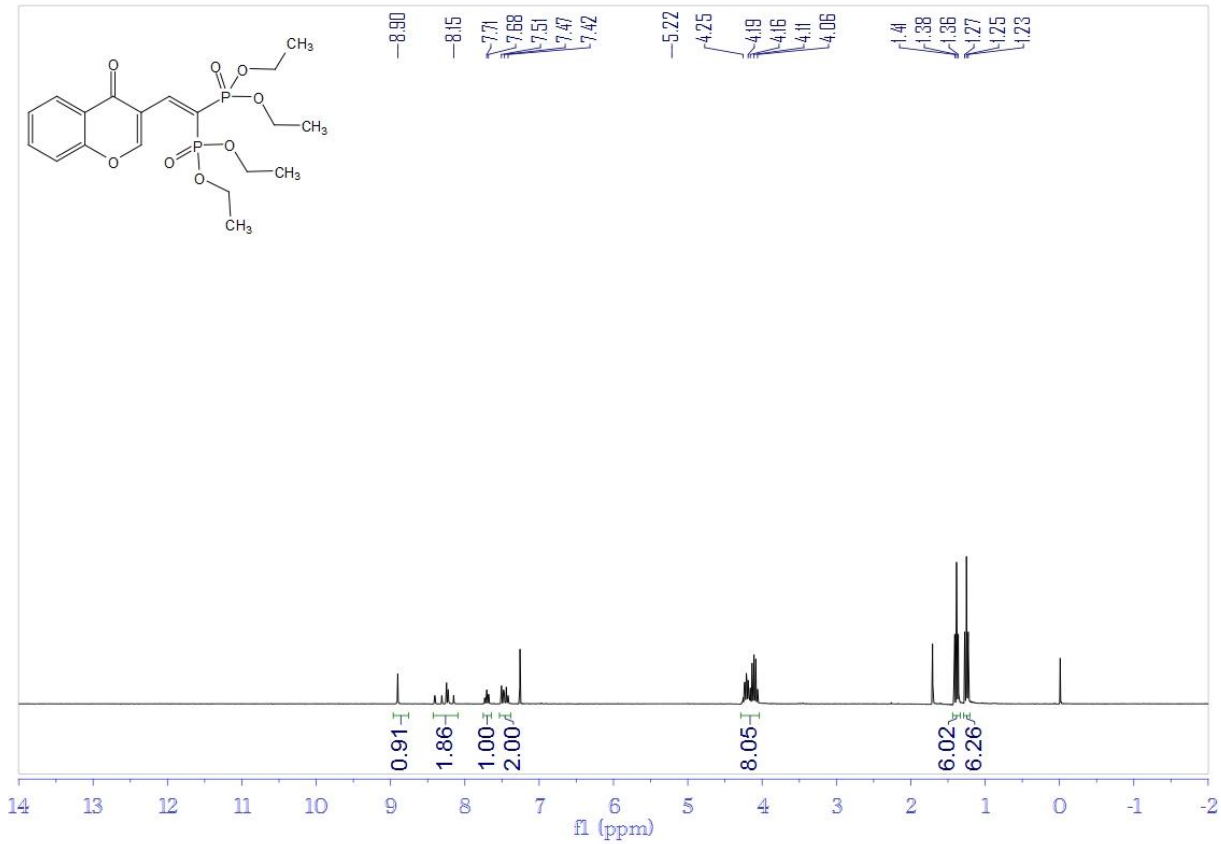


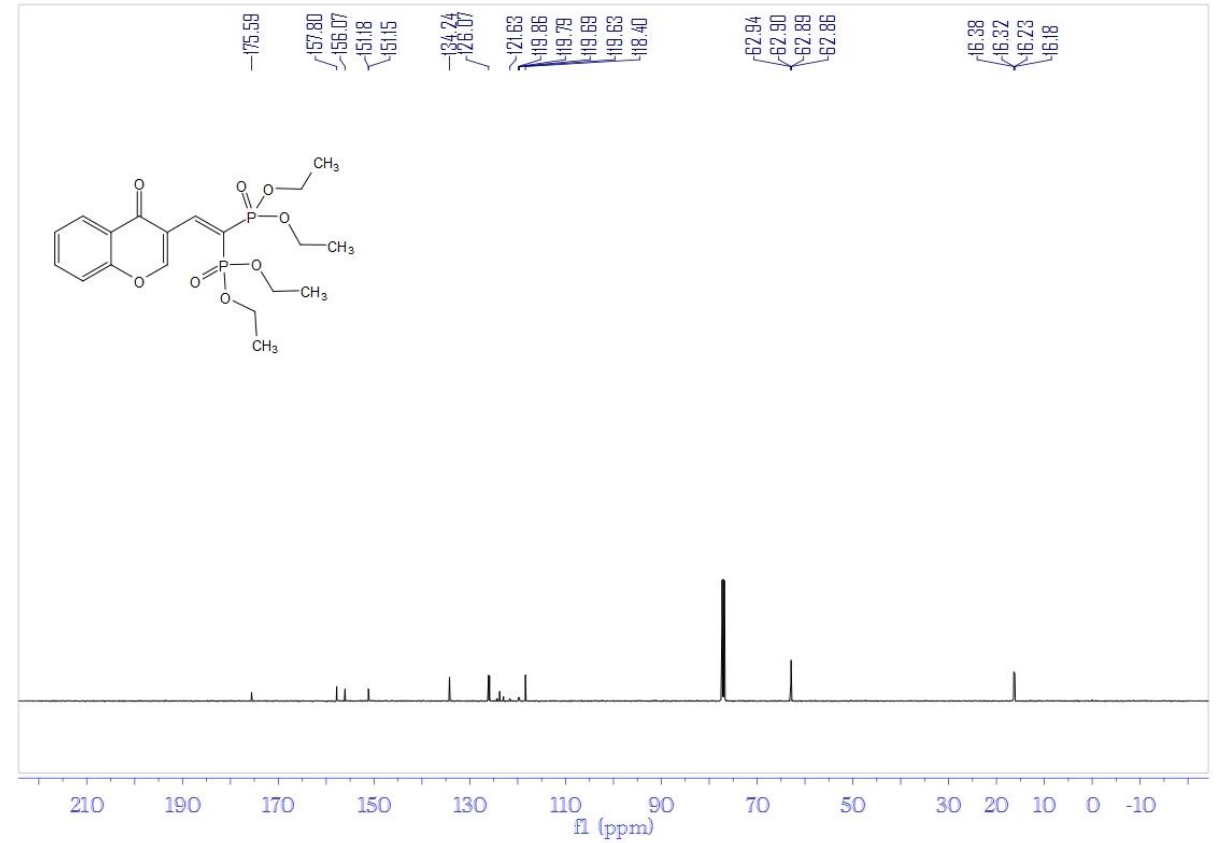
Compound **1** (0.2 mmol), NaOAc (0.24 mmol), and Hydrazine hydrochloride or hydrazine **2** (0.2 mmol) was dissolved in EtOH (5 mL)and the mixture was stirred at room temperature for hours, (monitored by TLC). The $NaBH_4$ (0.6 mmol) was added after the compound **1** was completely converted to the intermediate. Then, the ethanol was evaporated under reduce pressure after stirring at room temperature for another 3 hours. The residue was partitioned between 1 M HCl and EtOAc (20 mL). The layer of HCl was extracted with ethyl acetate (20 mL) twice. Combined the organic layer, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure, the rude product was obtained and further purified by column chromatography (CH_2Cl_2: MeOH 100:0 - 30:1).

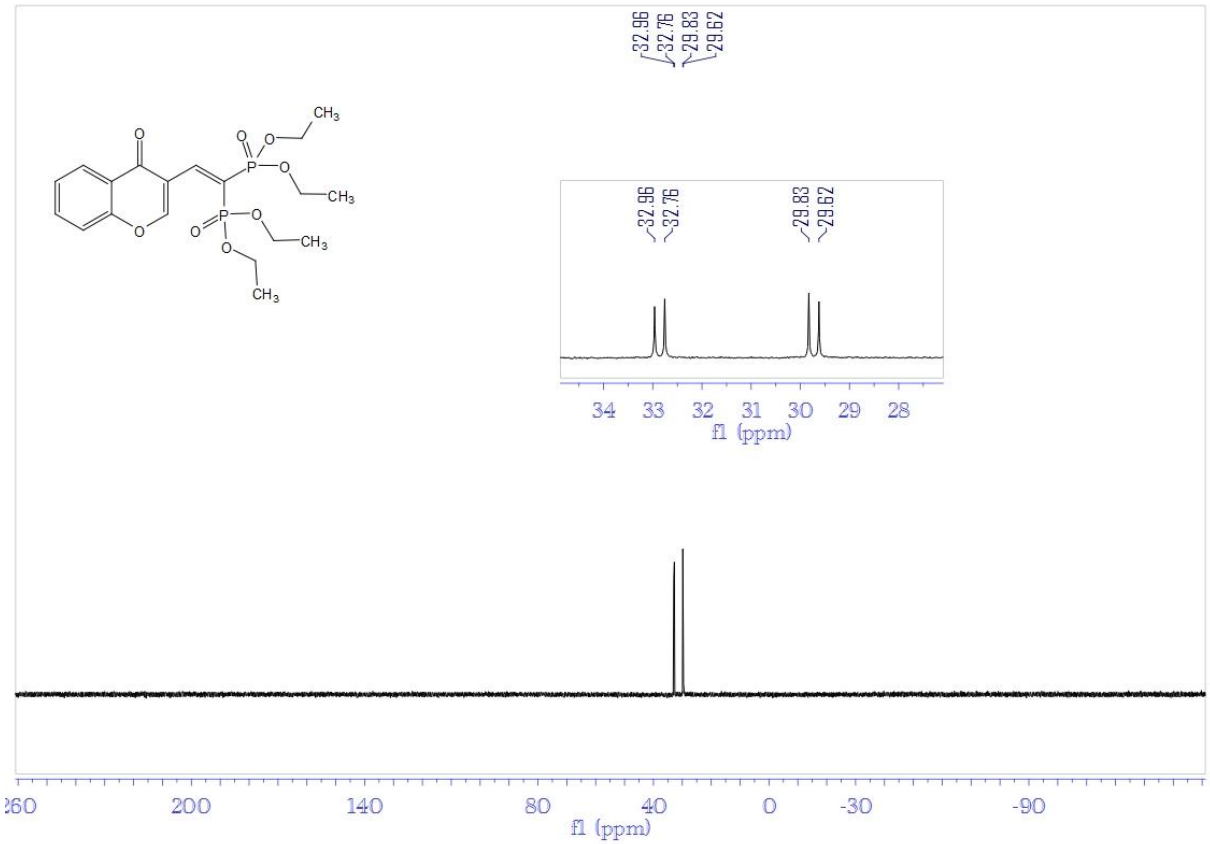
2. ^{1}H NMR, ^{13}C NMR and ^{31}P NMR

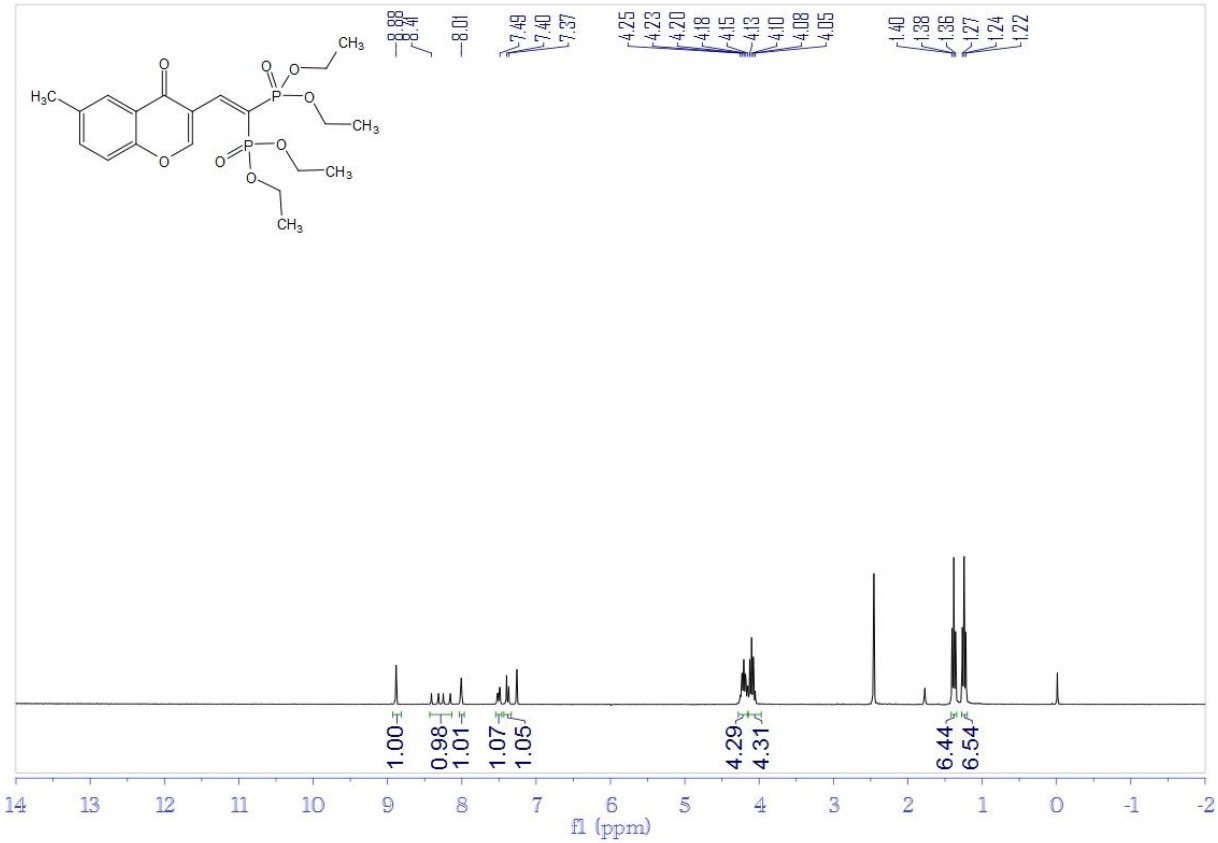


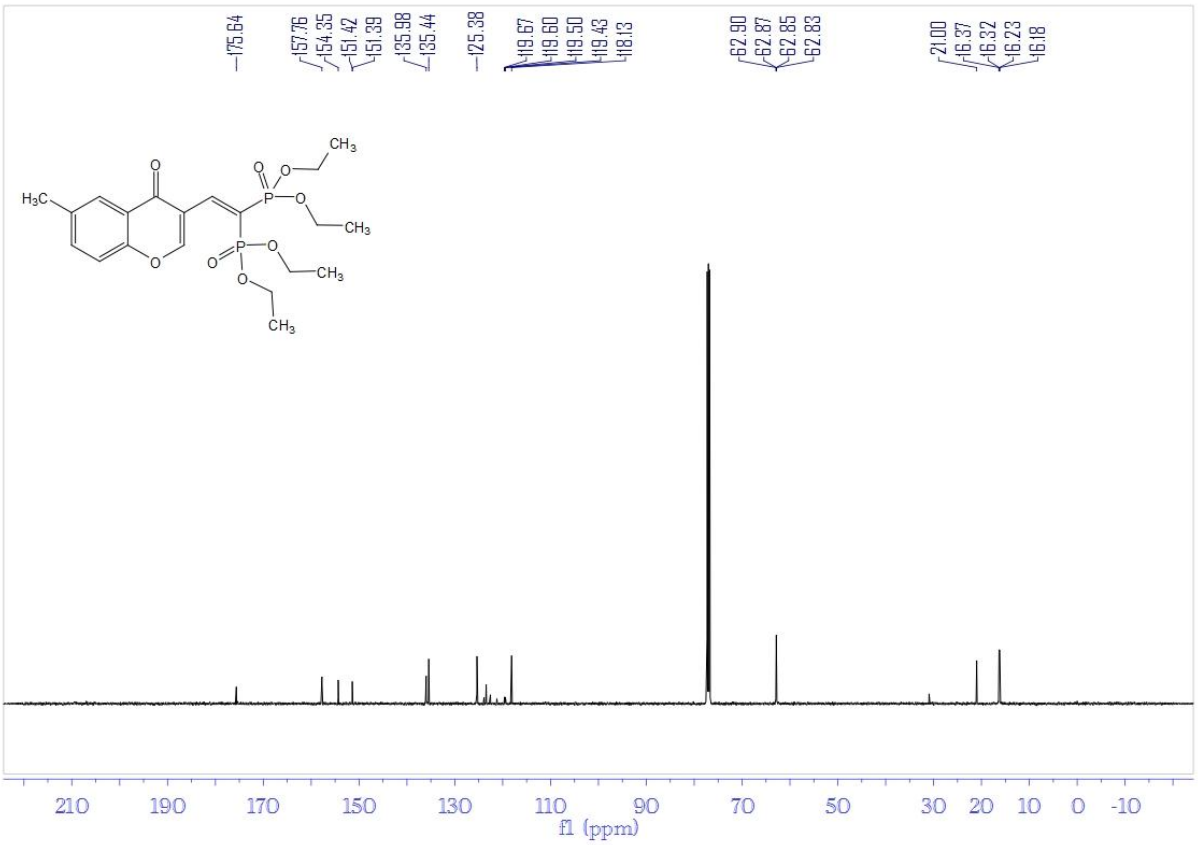


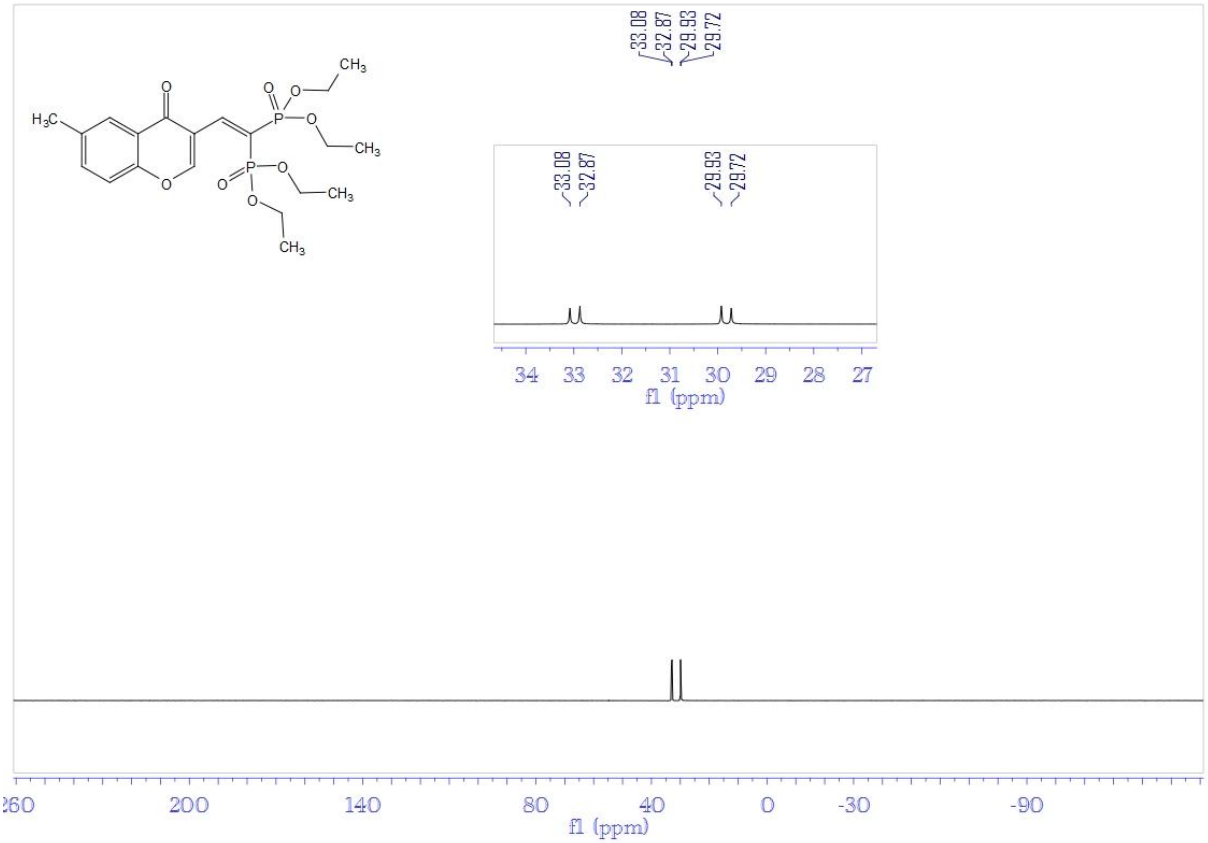


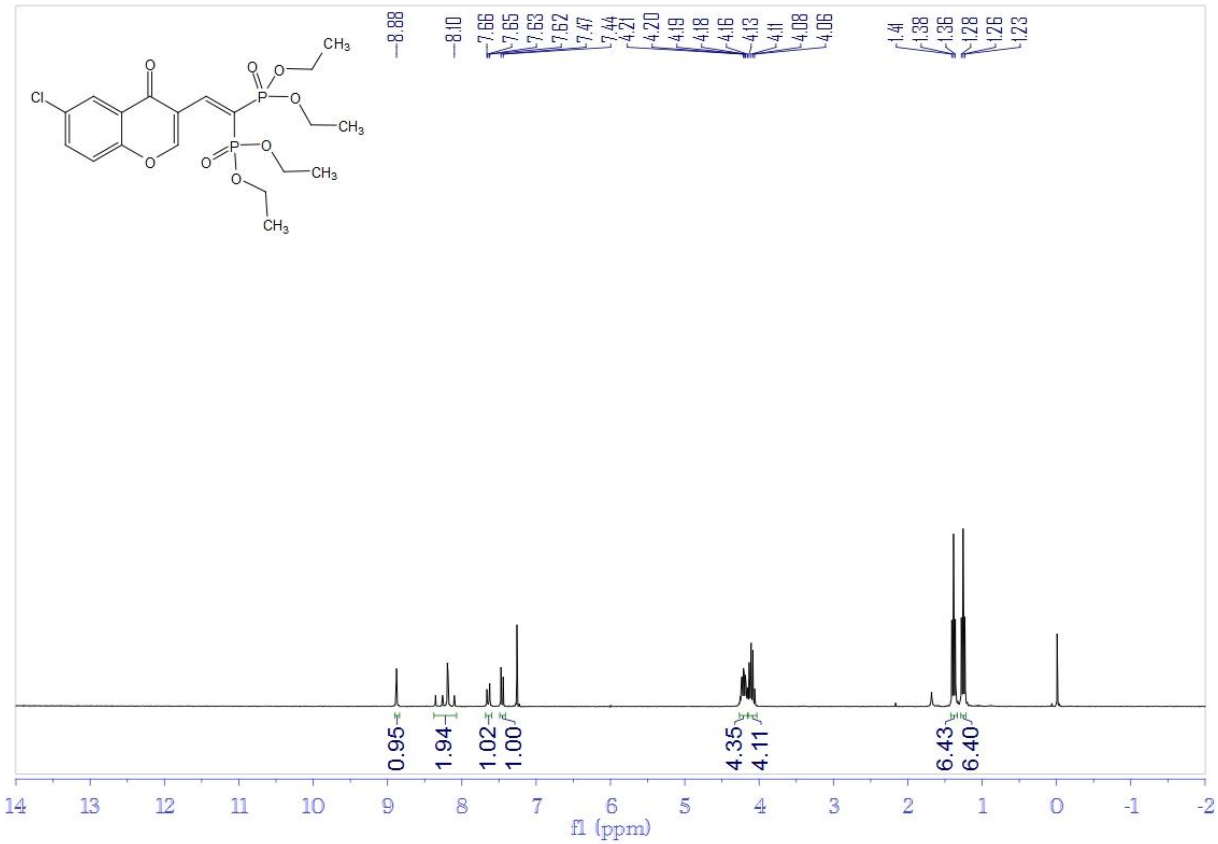








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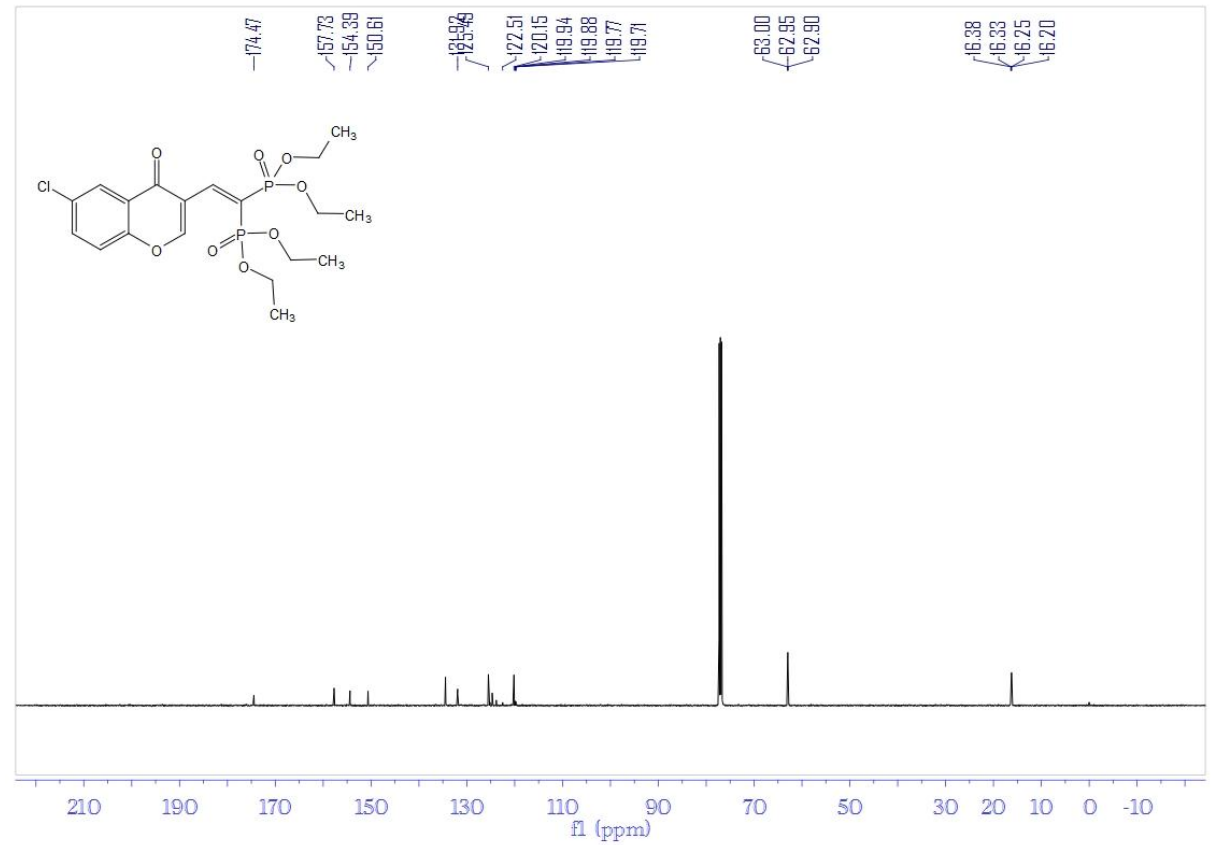
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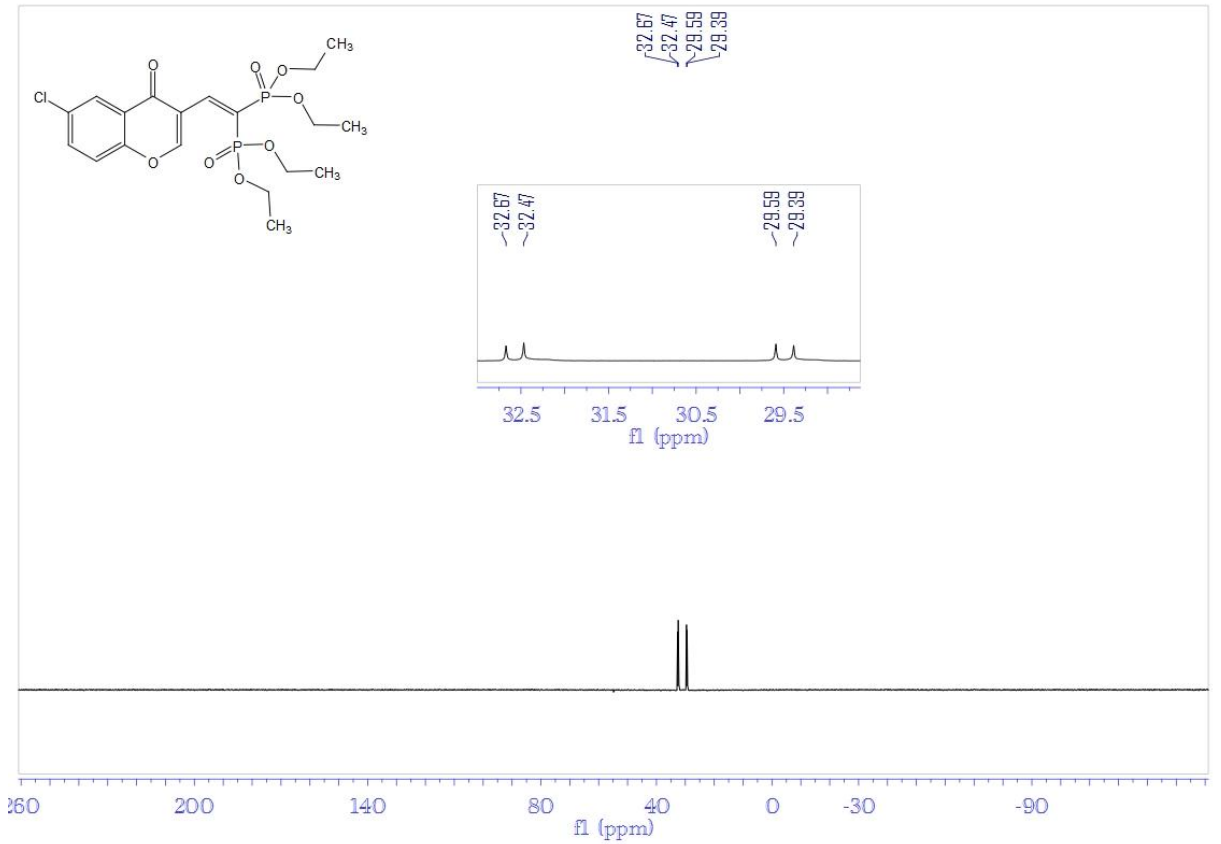

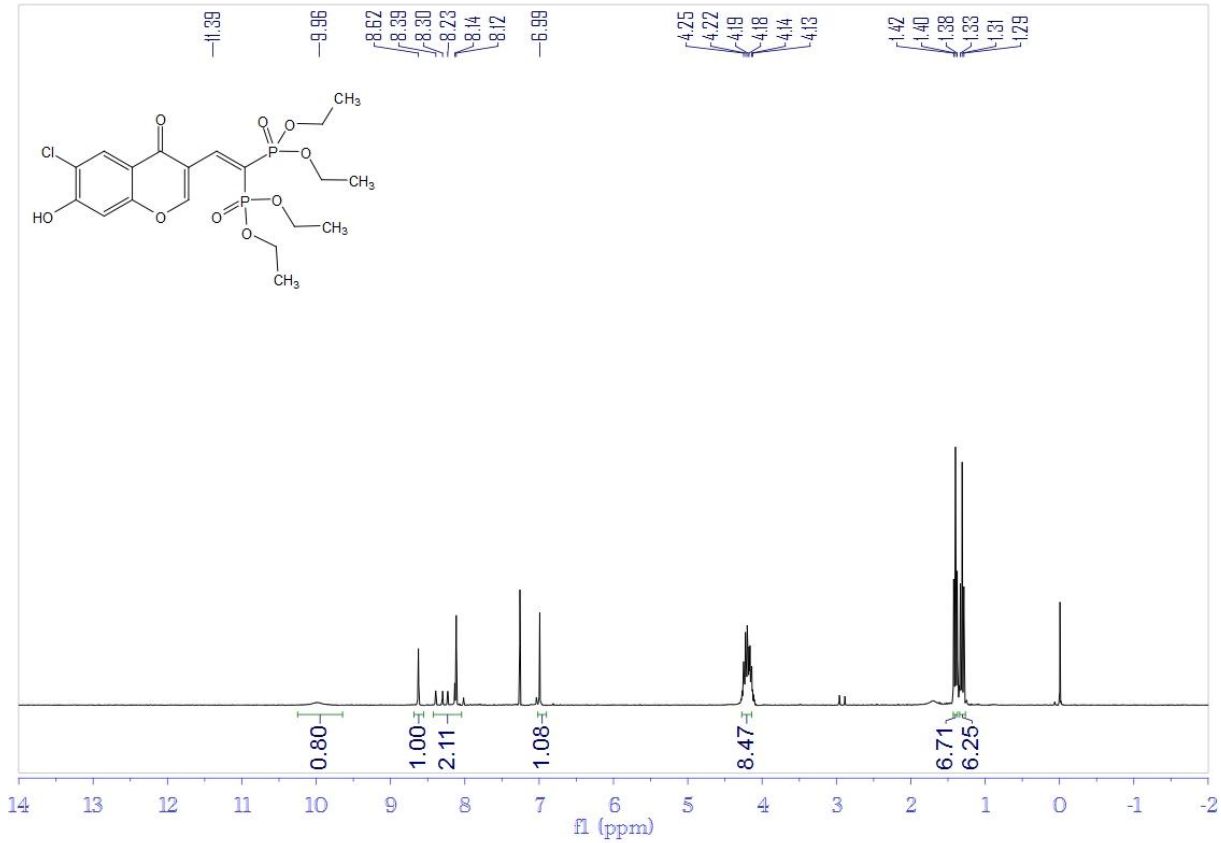

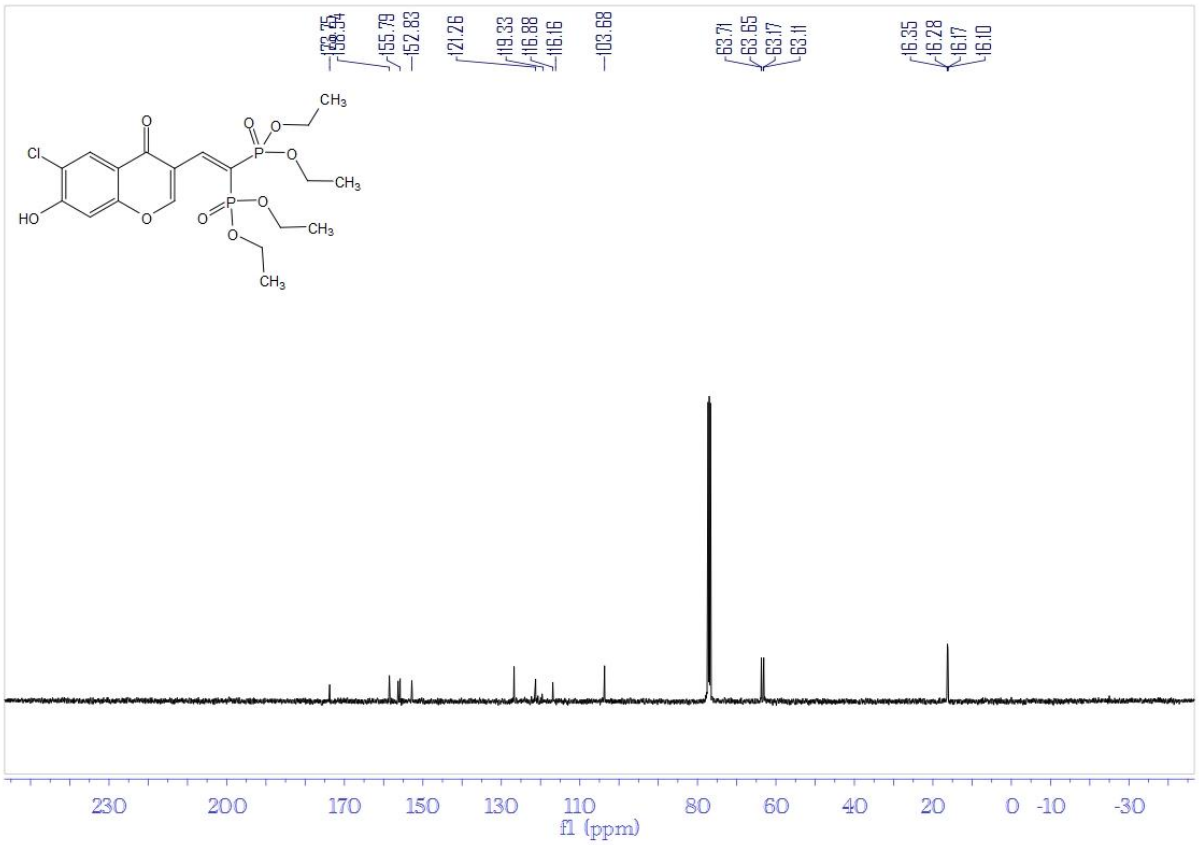
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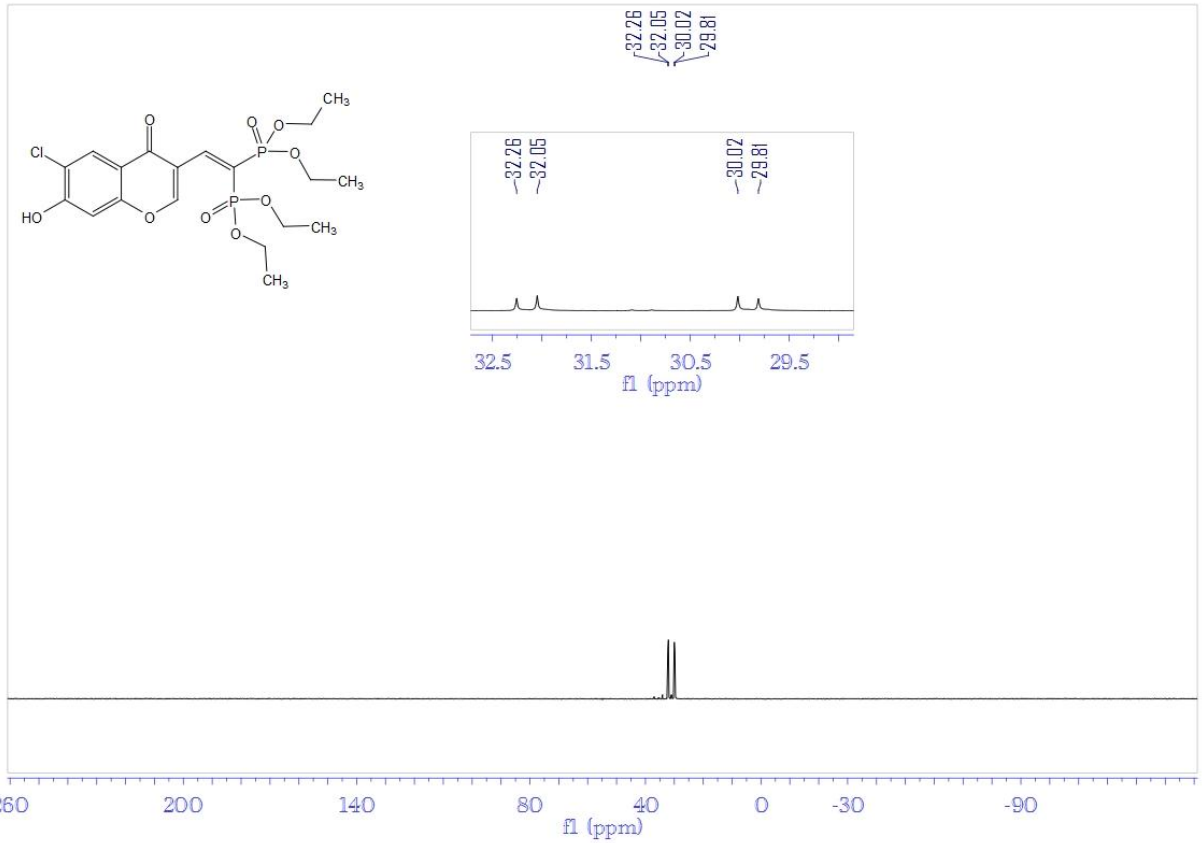
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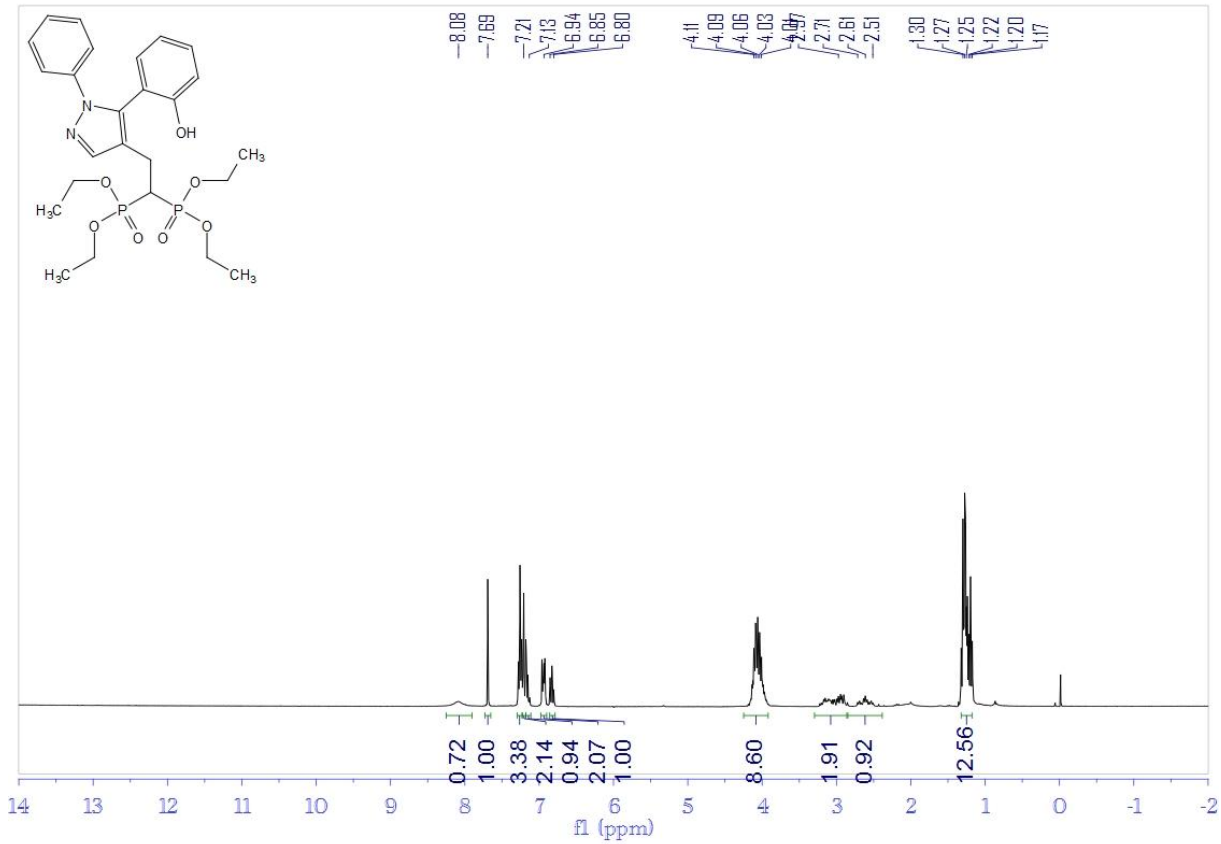

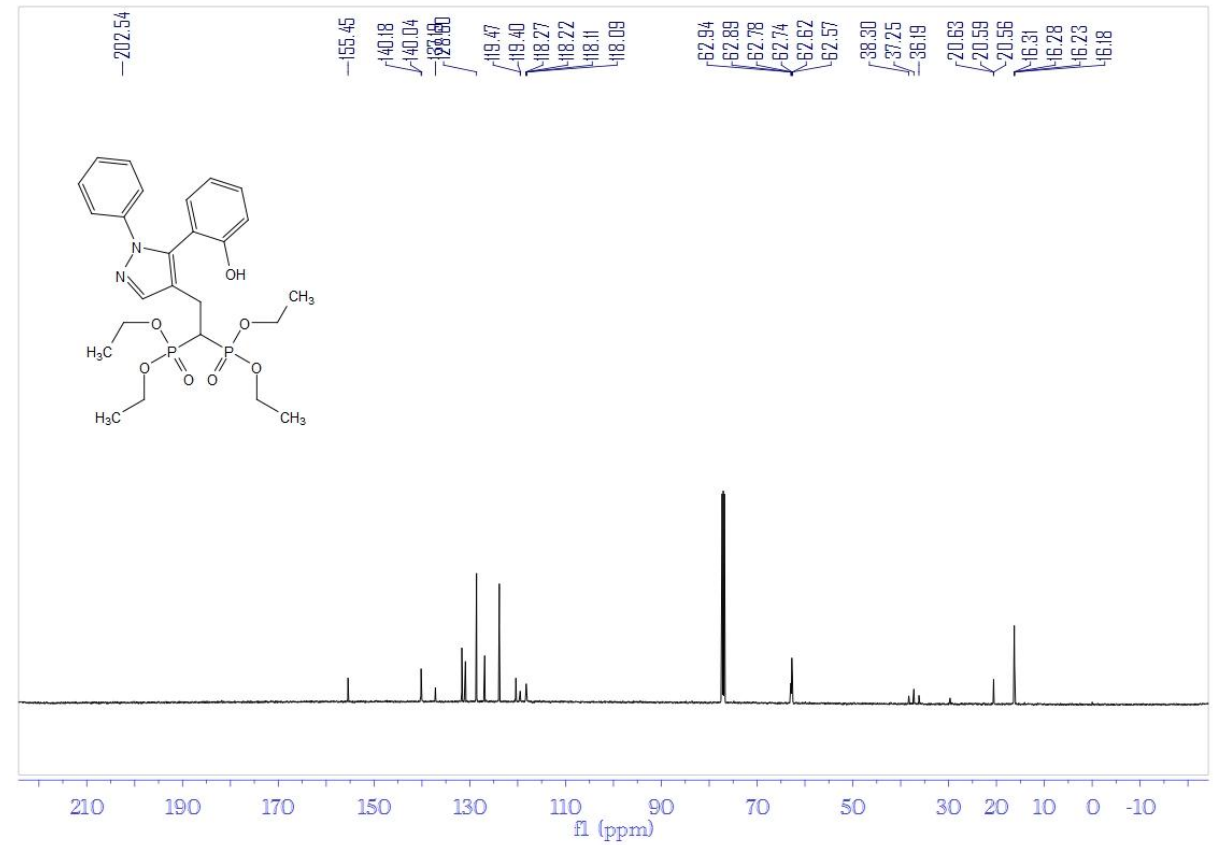

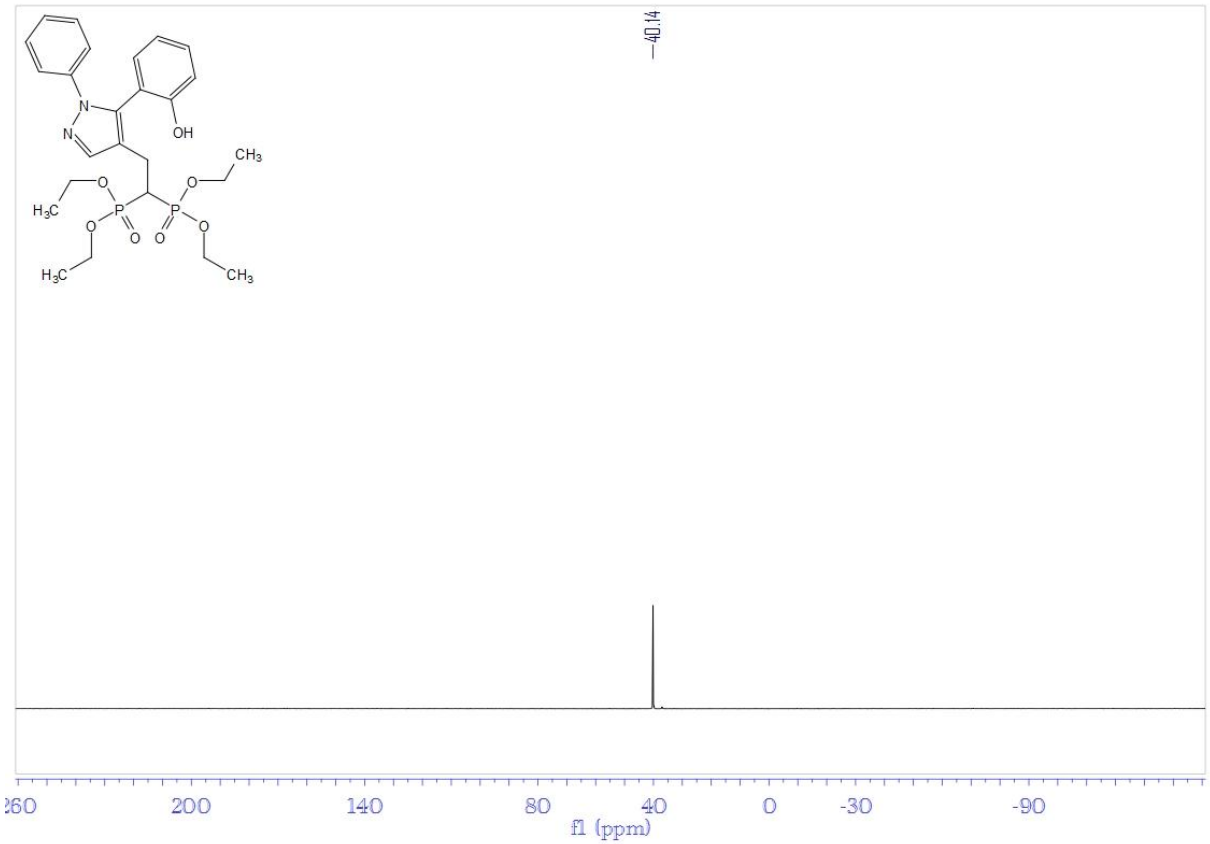

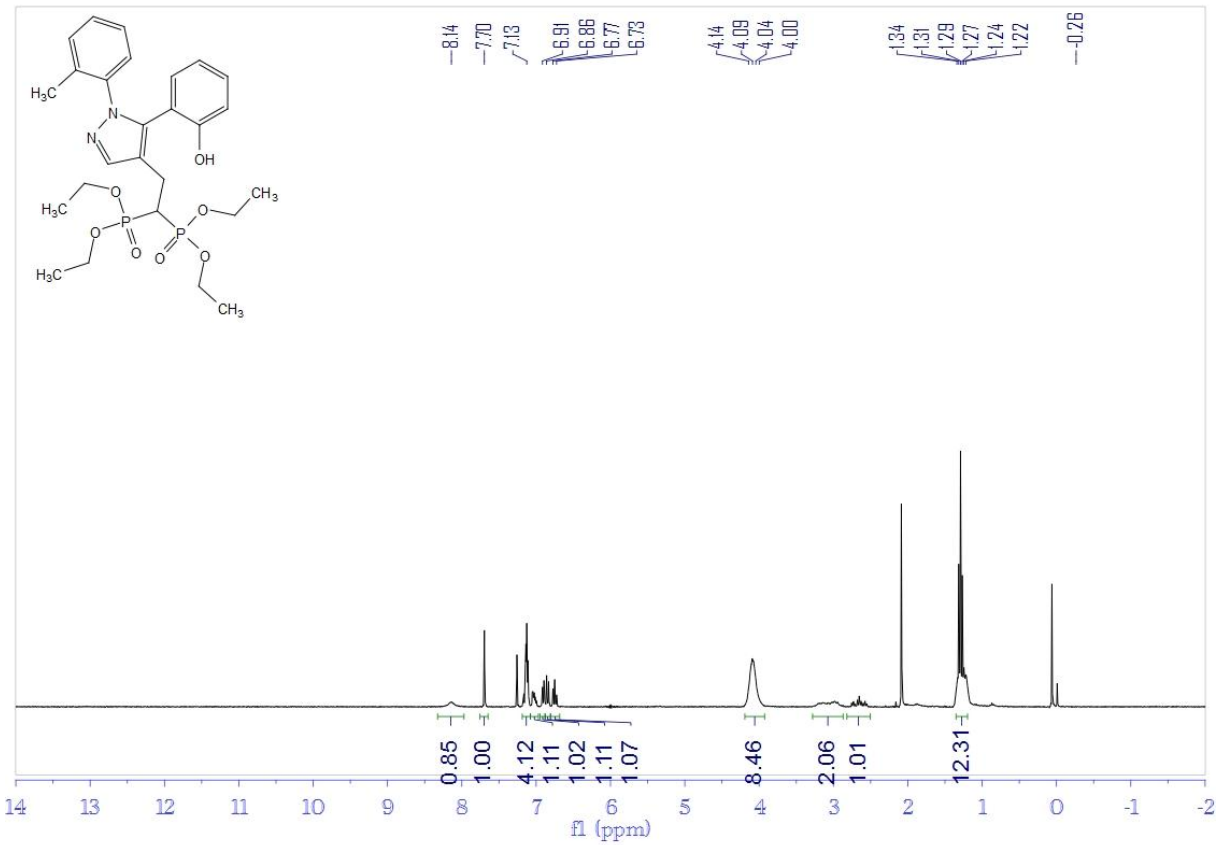

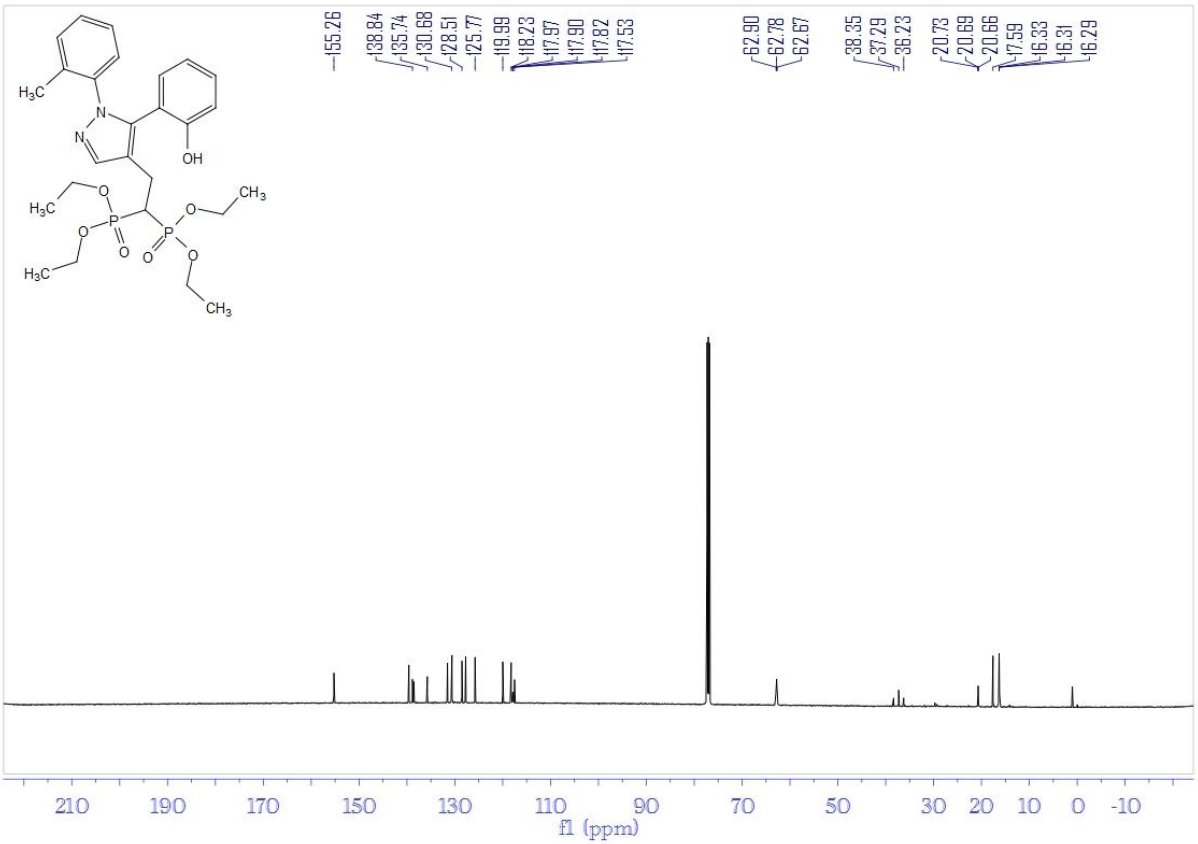
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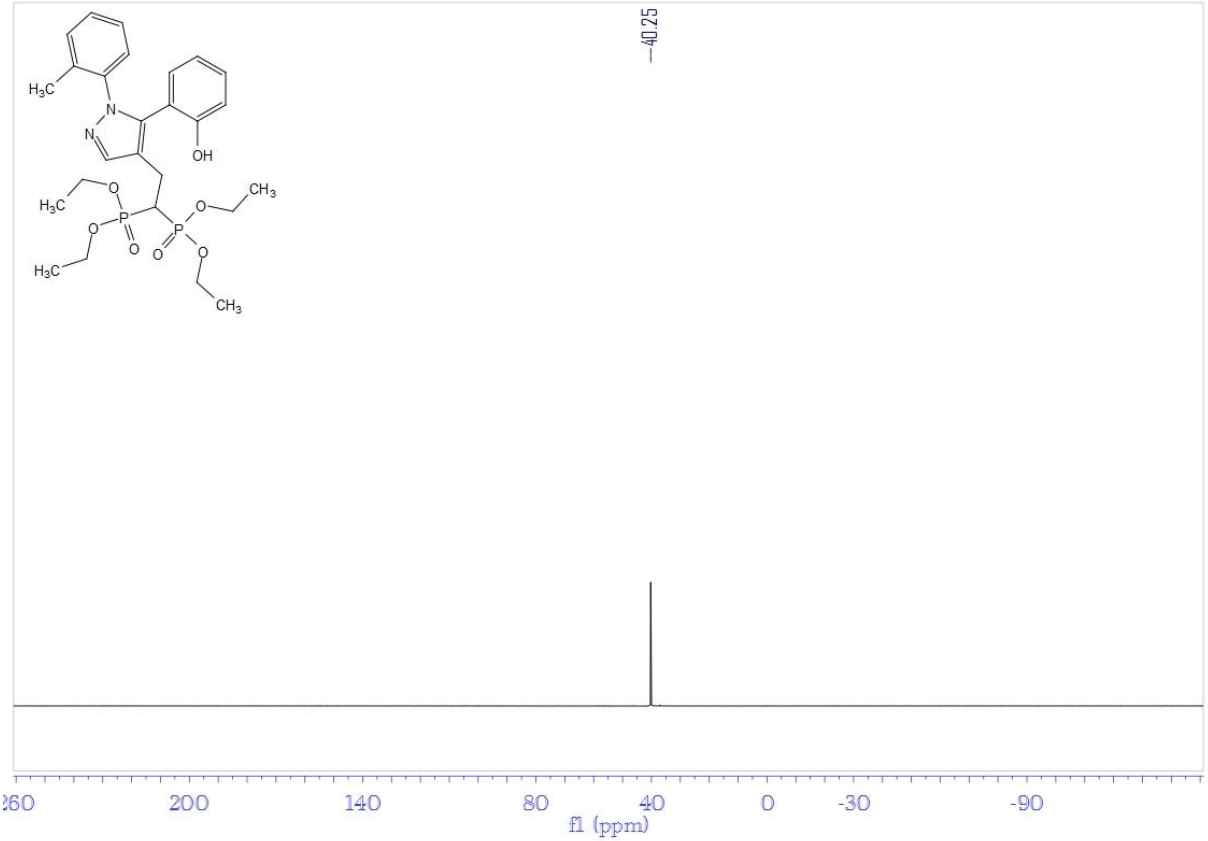
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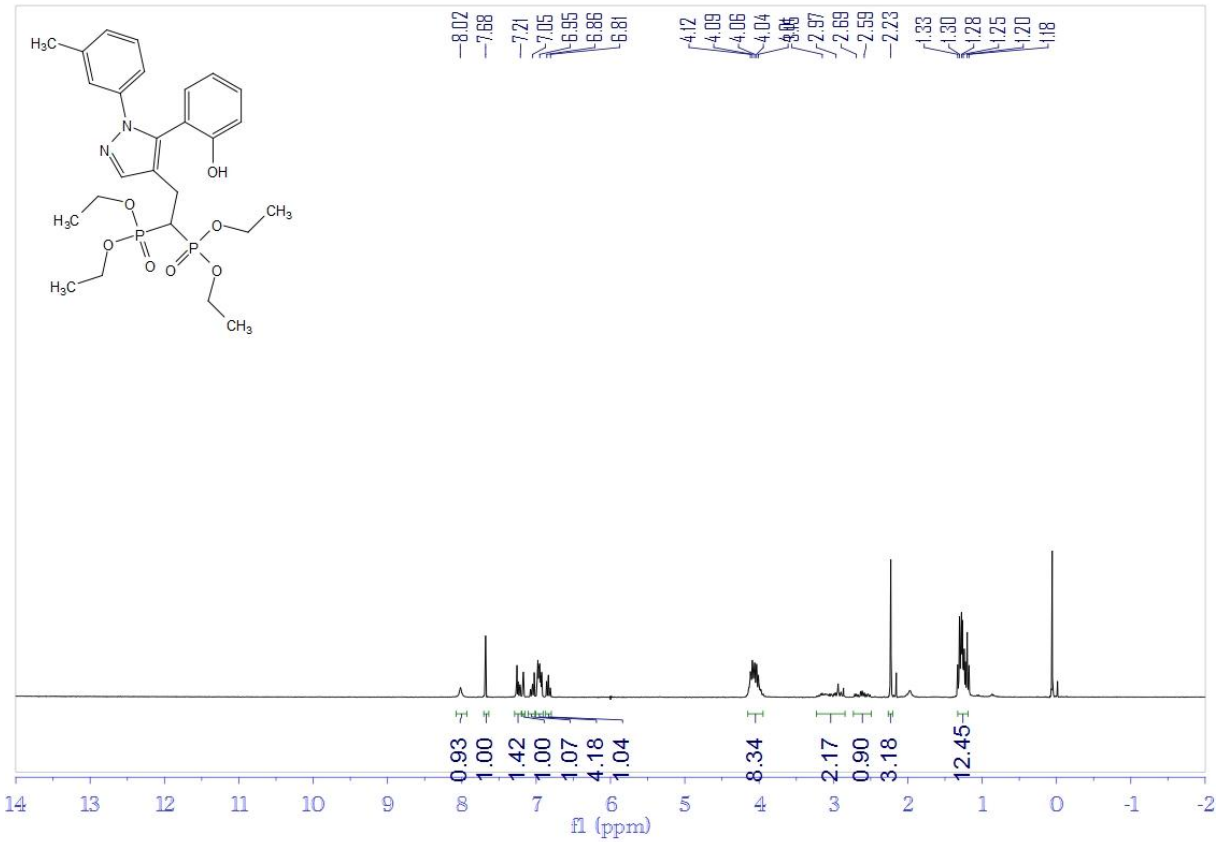

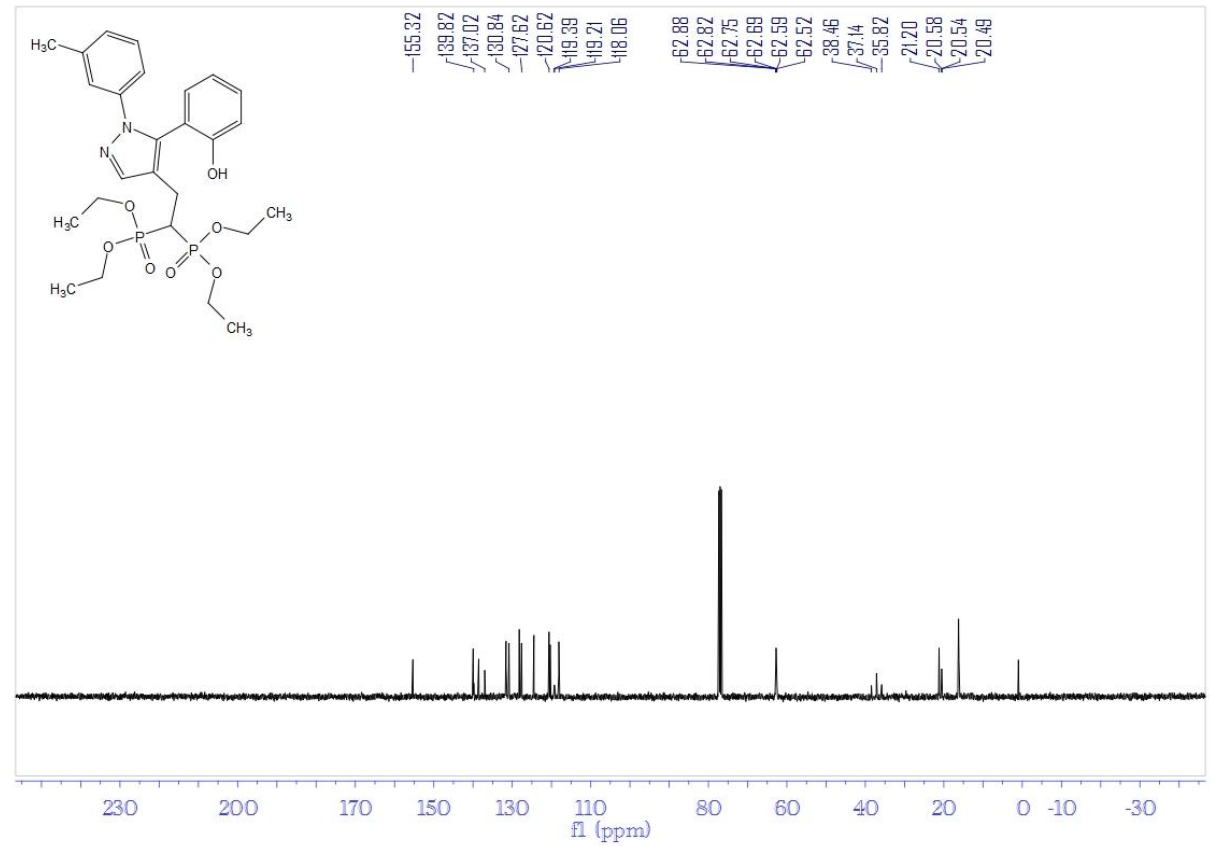


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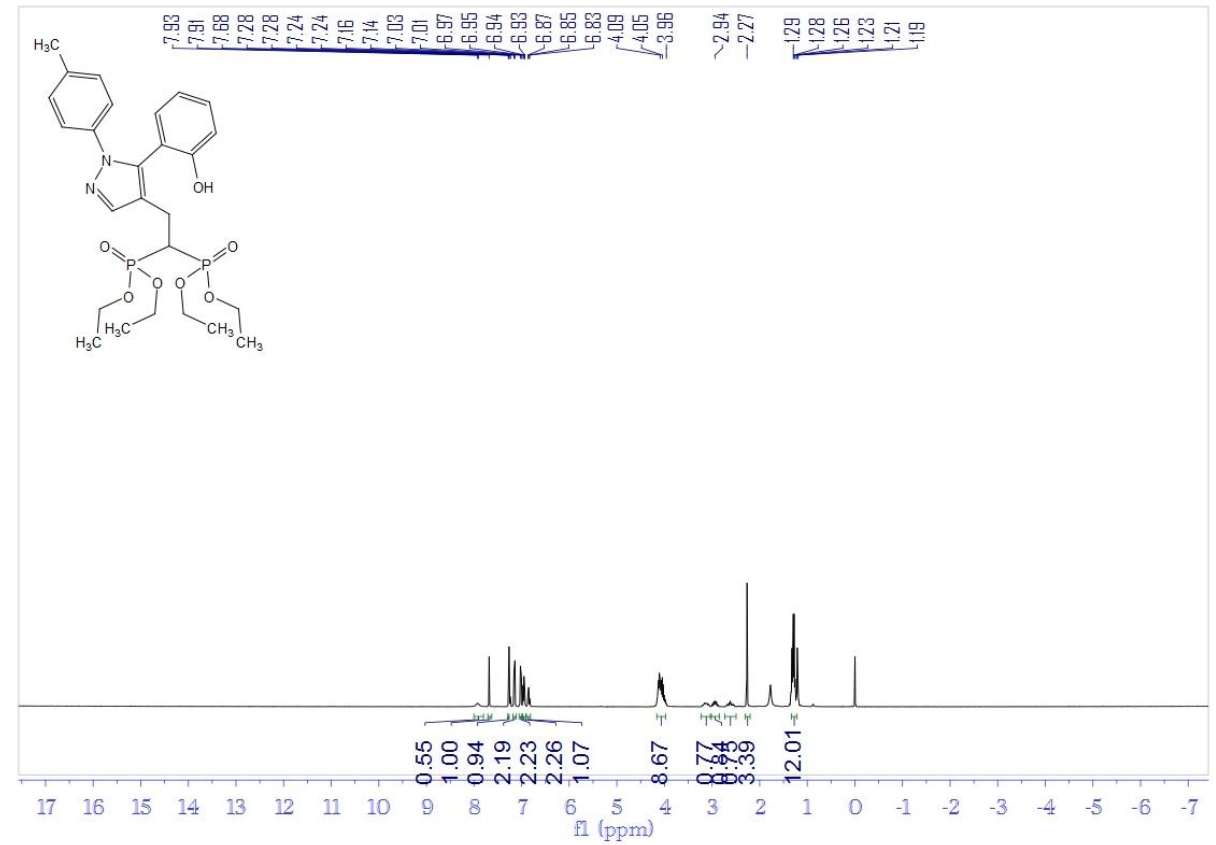
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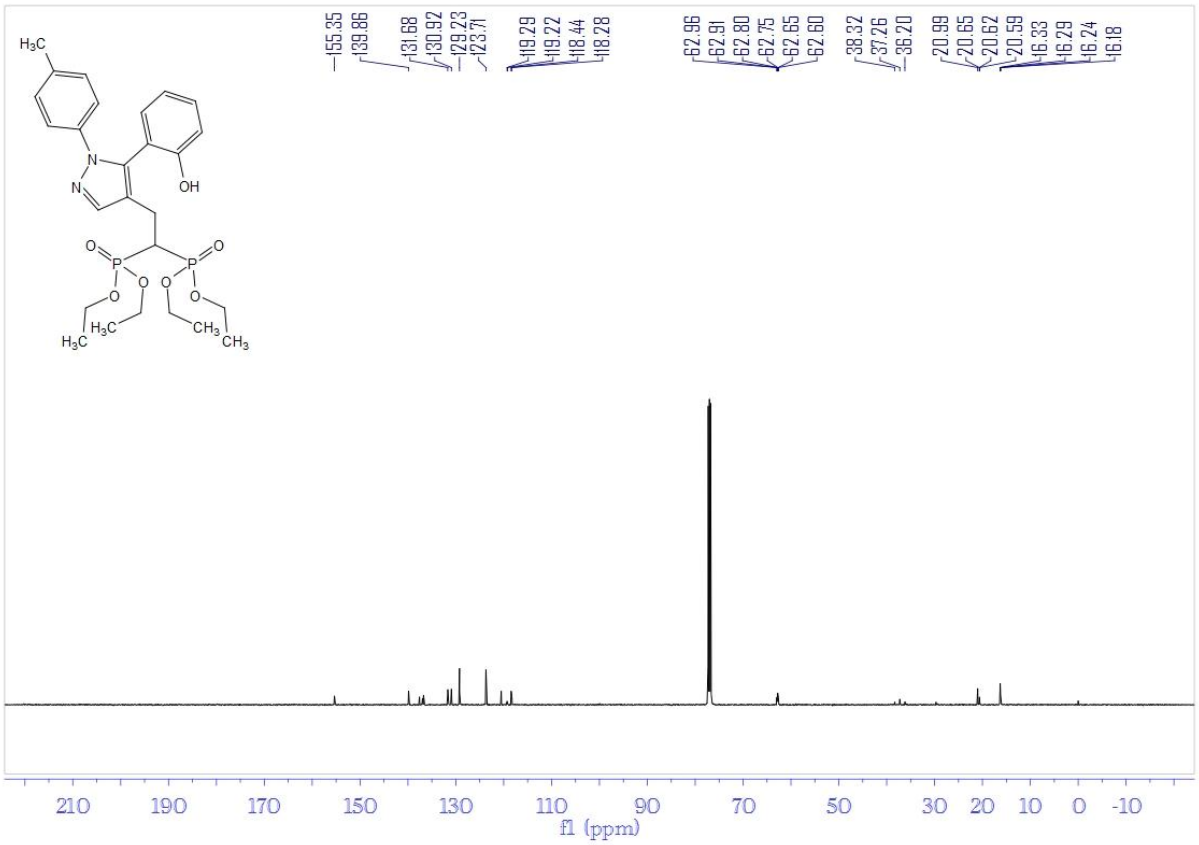
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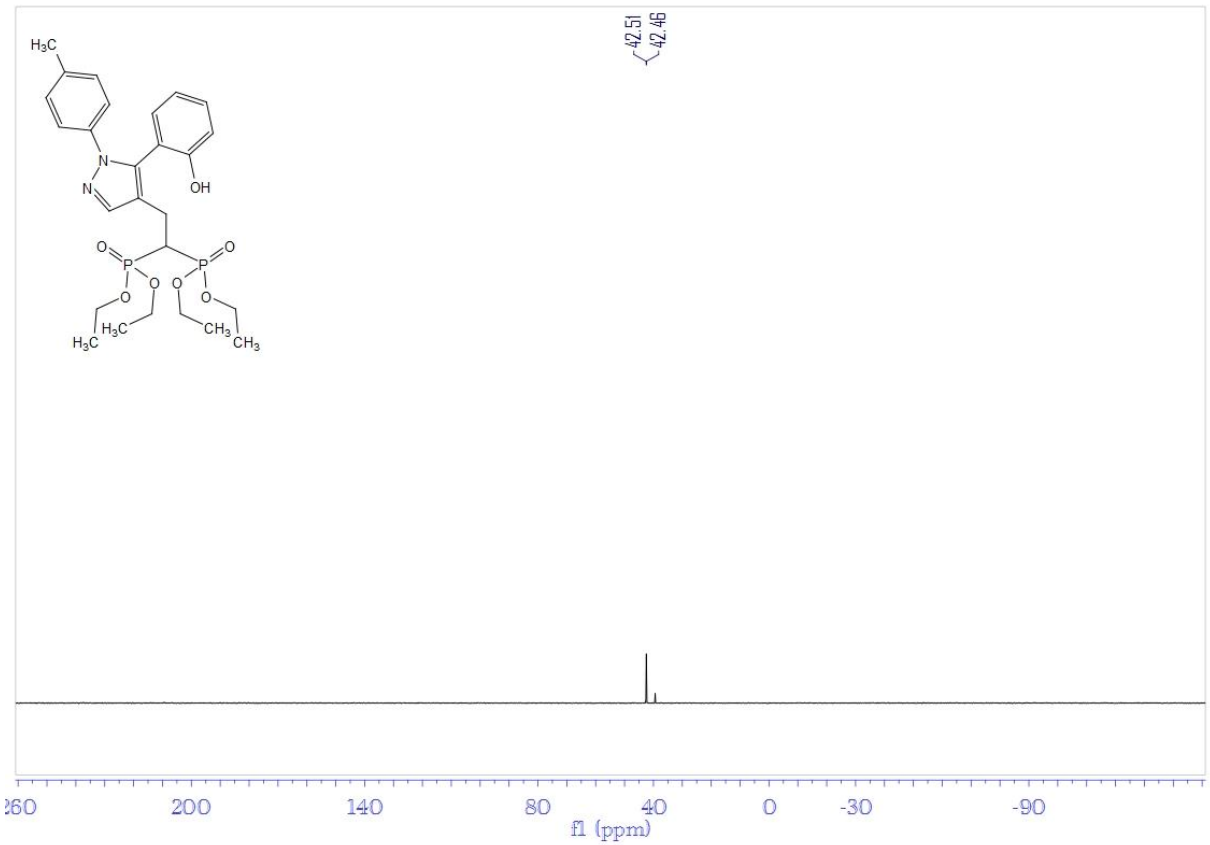
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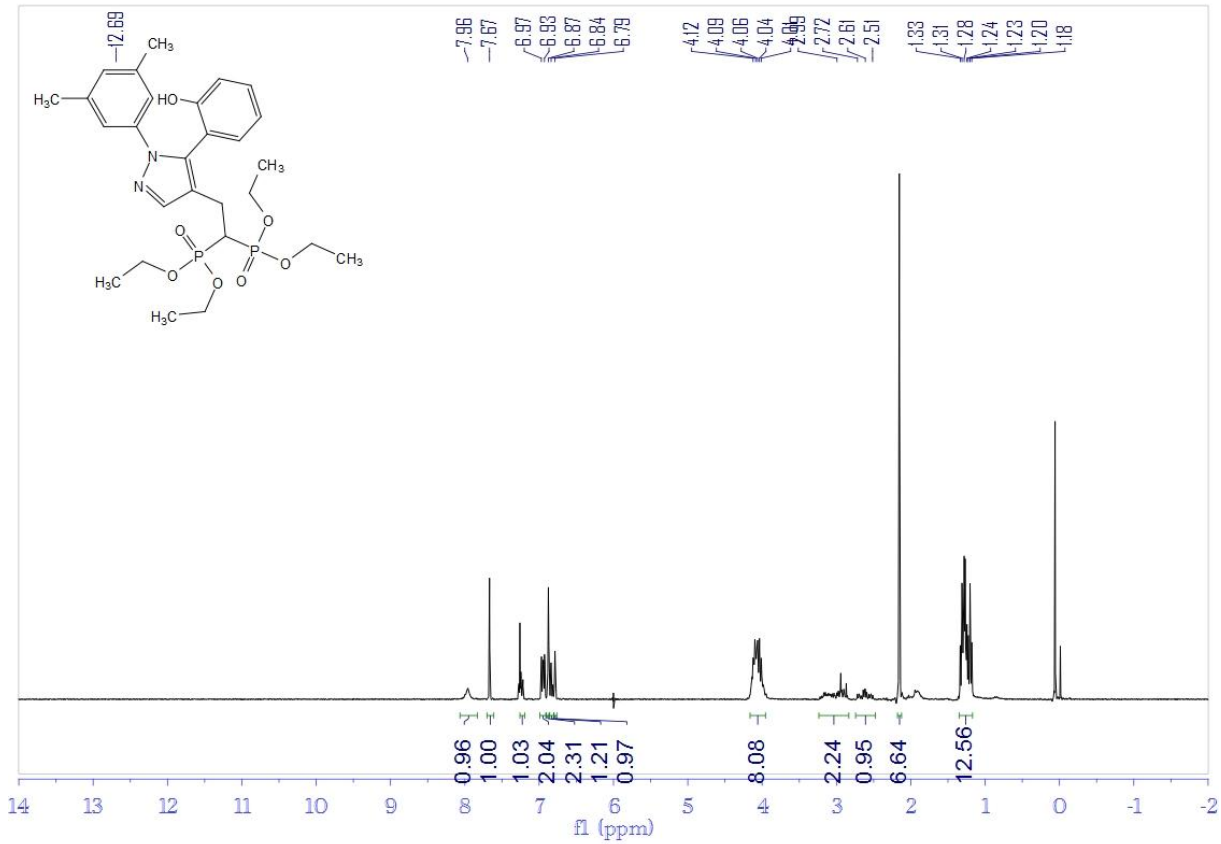
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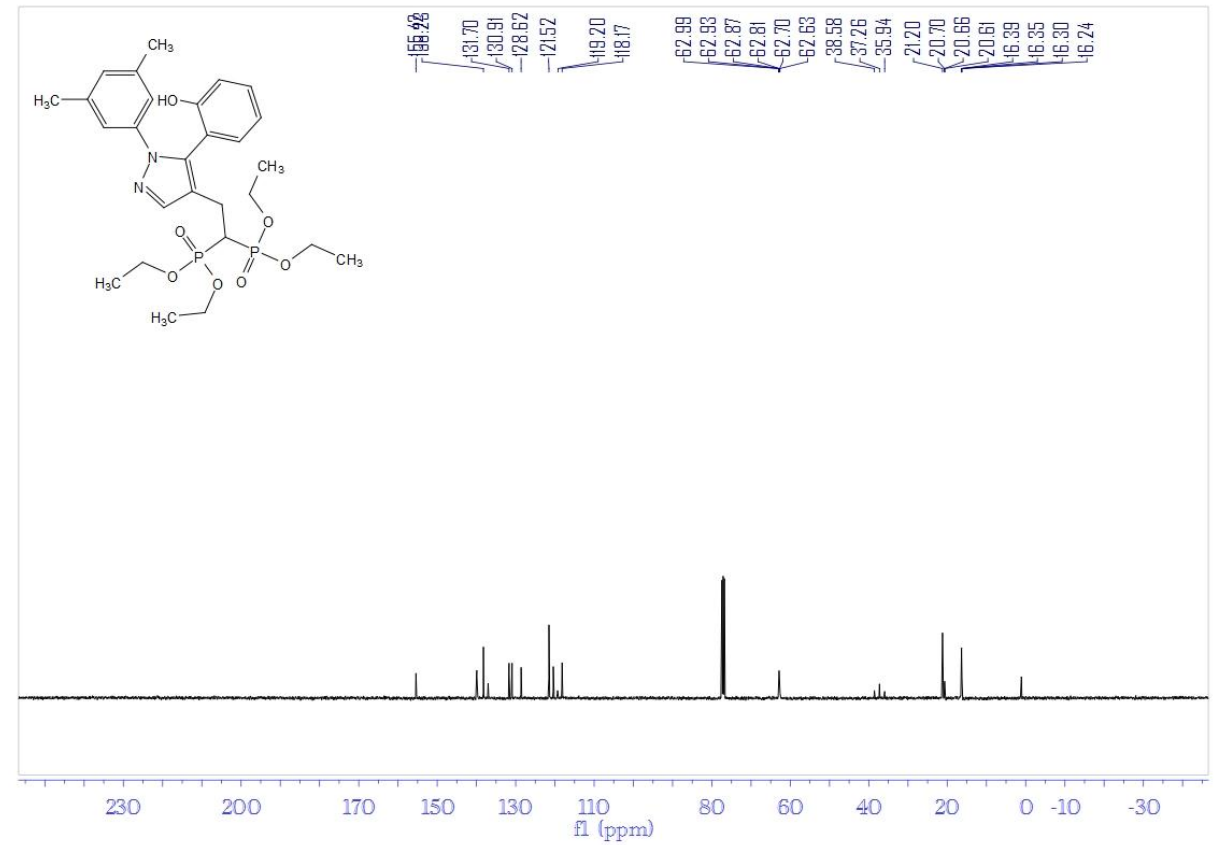
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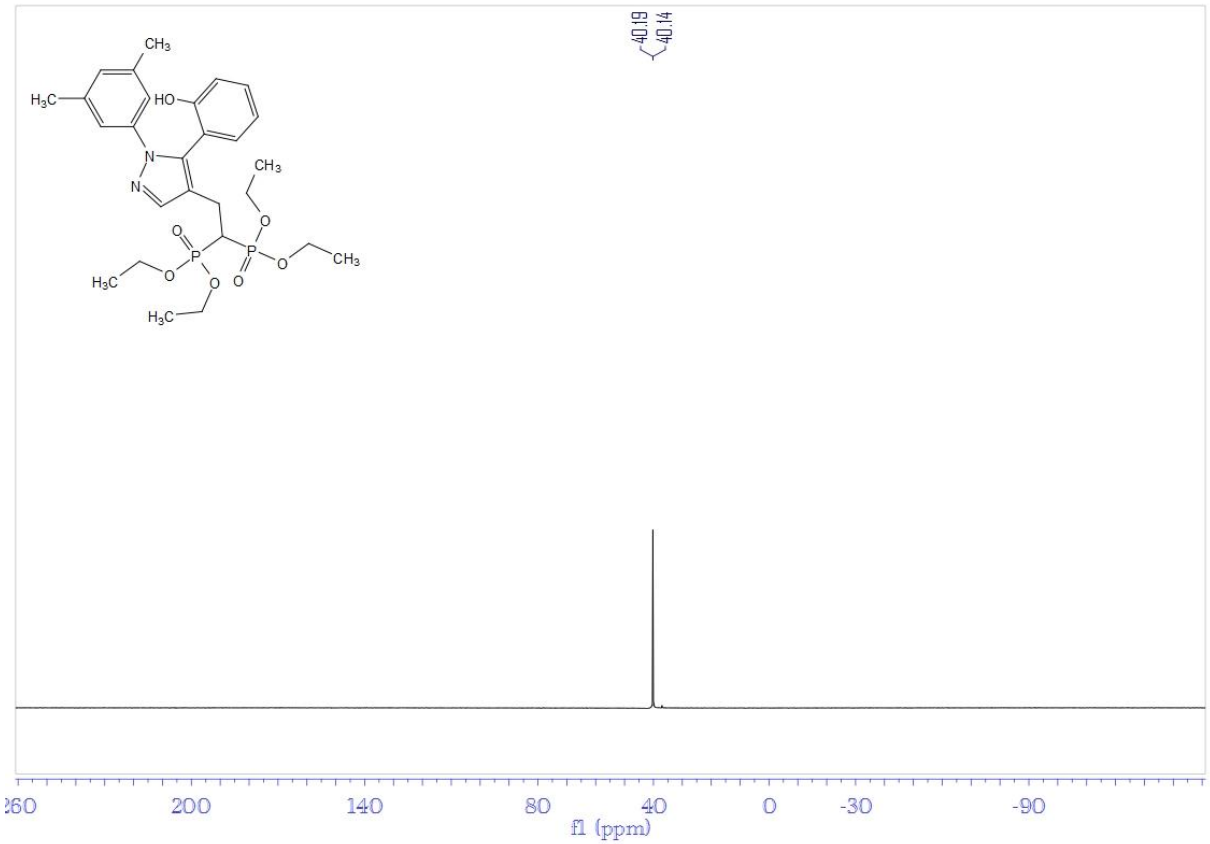
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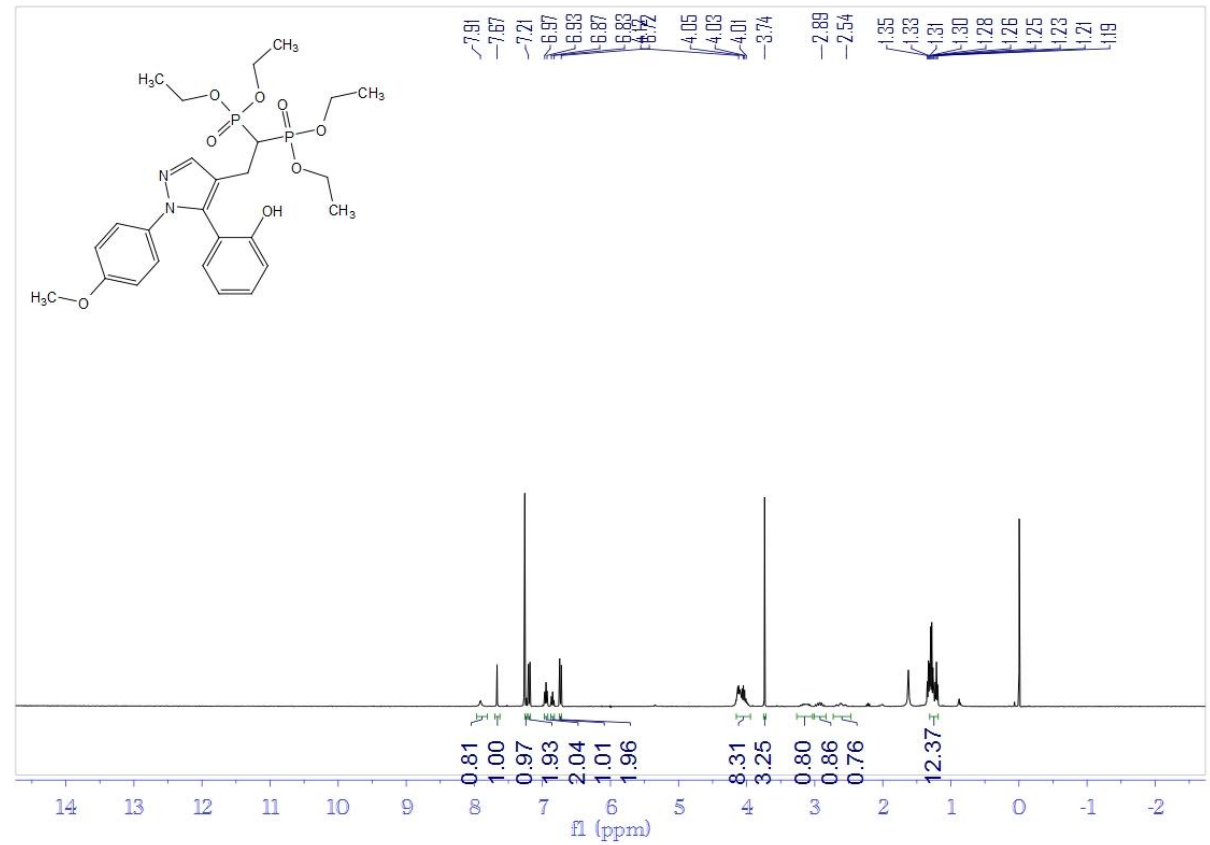
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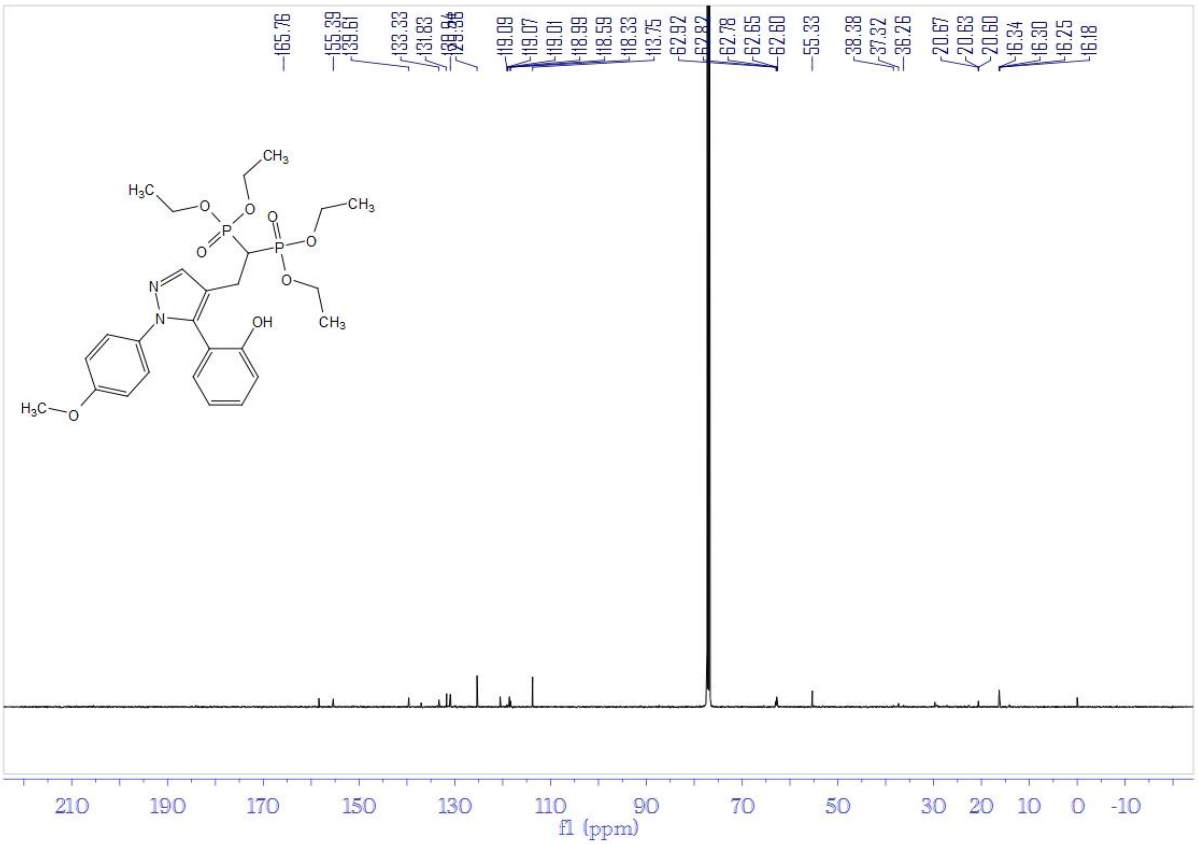
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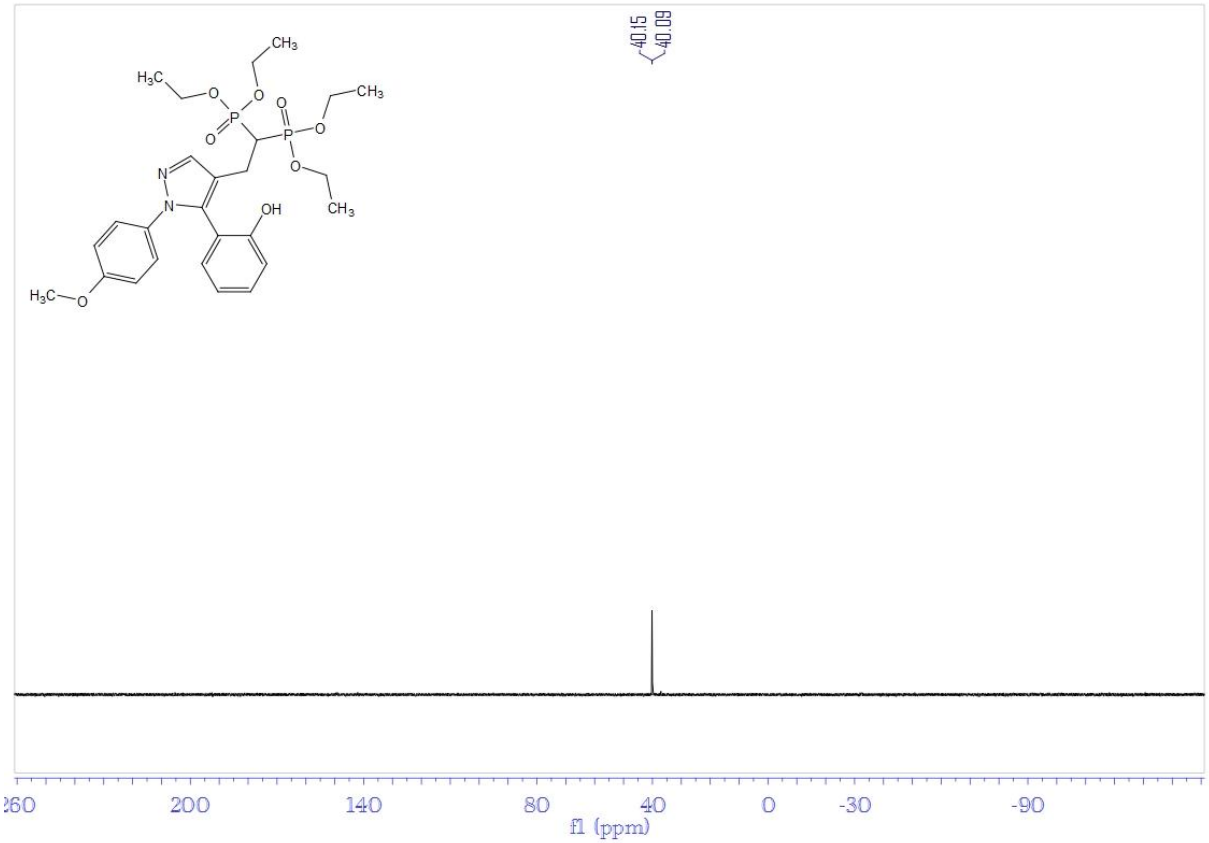
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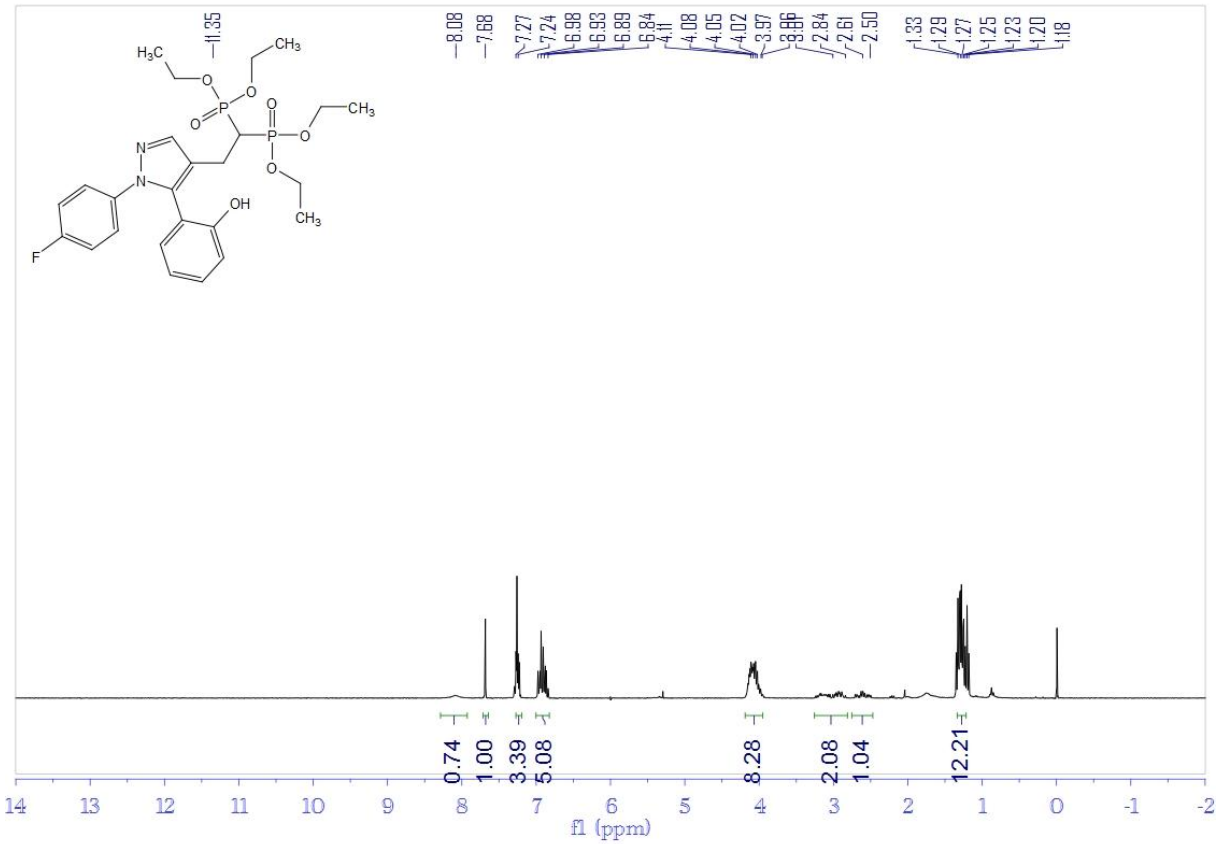
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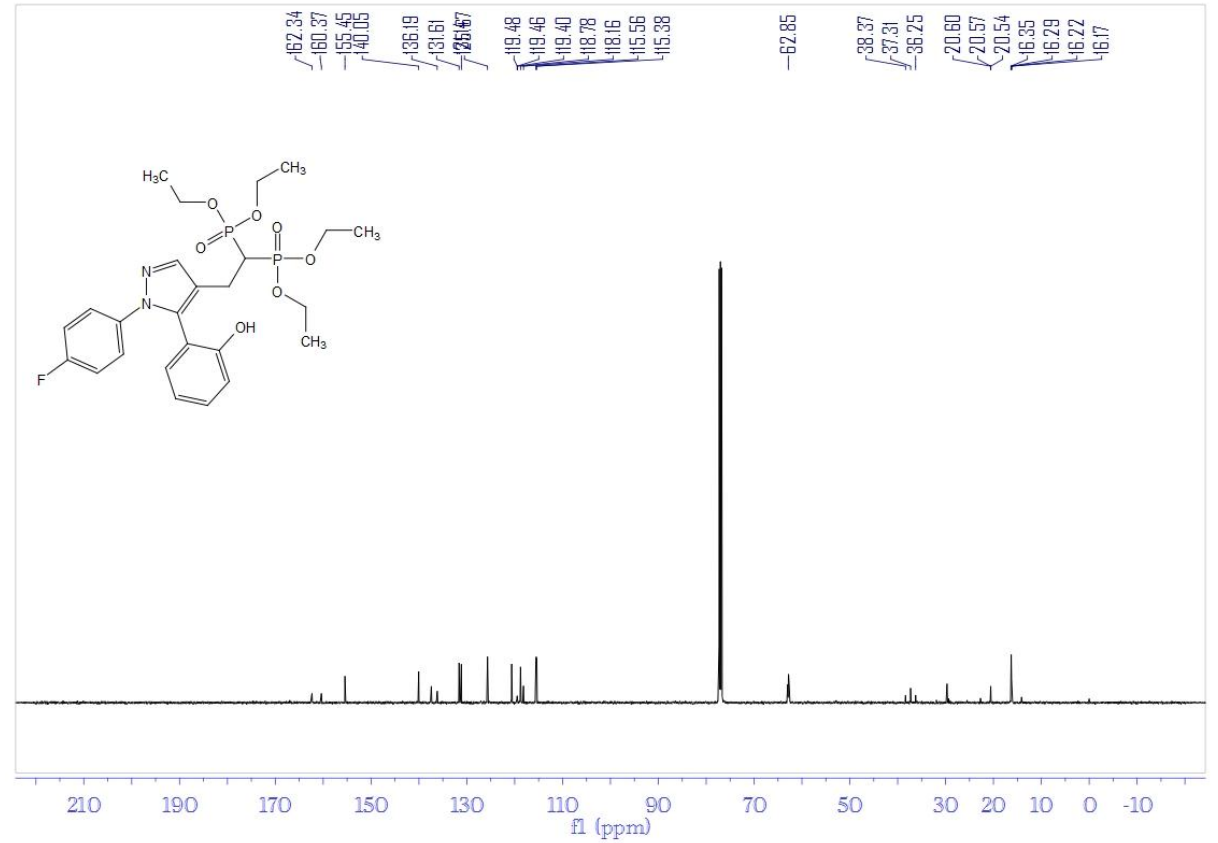
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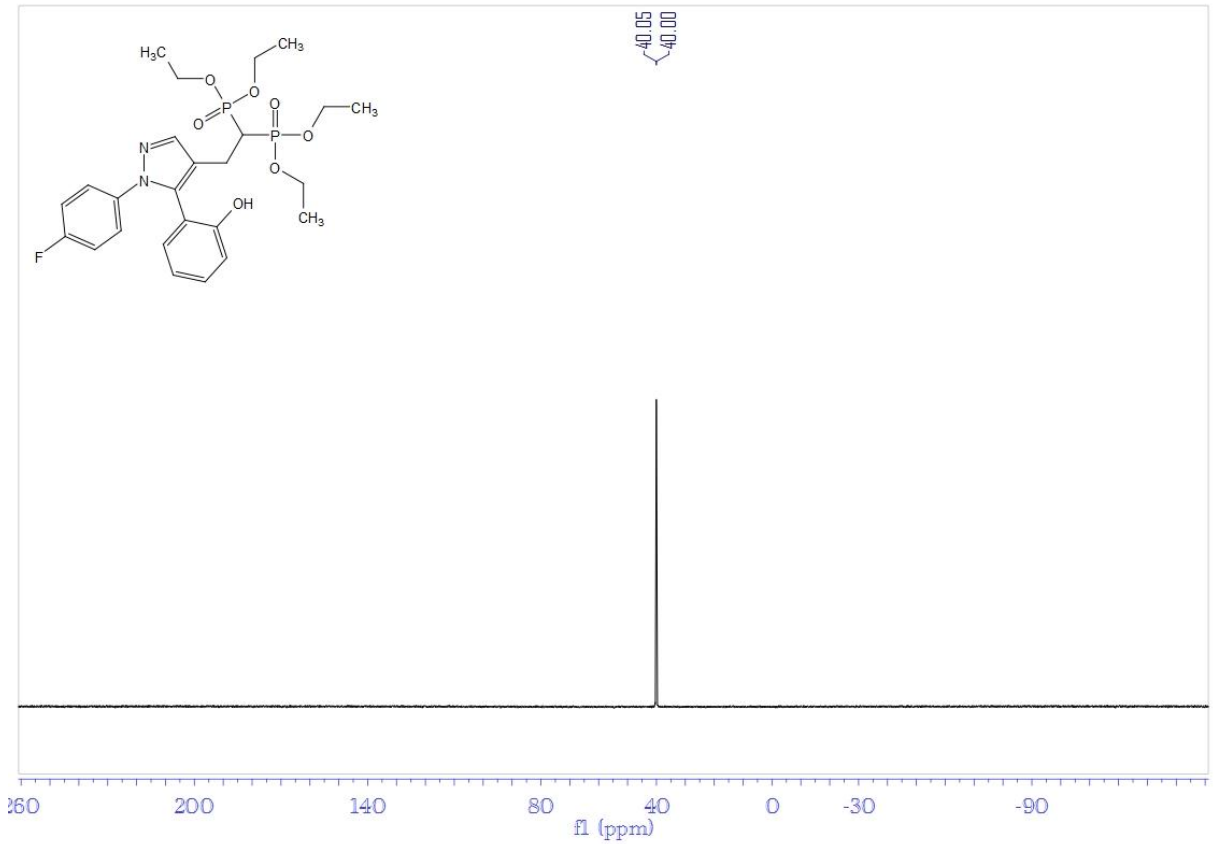

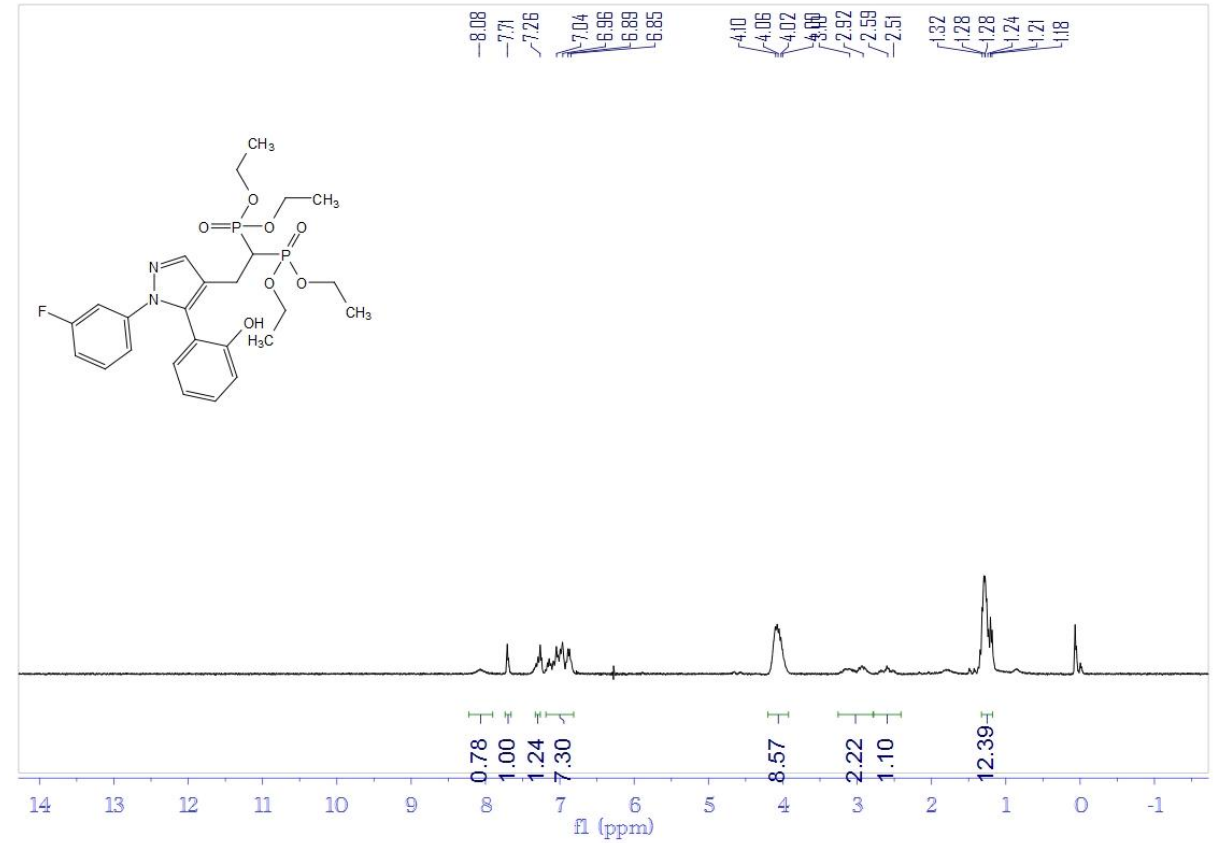

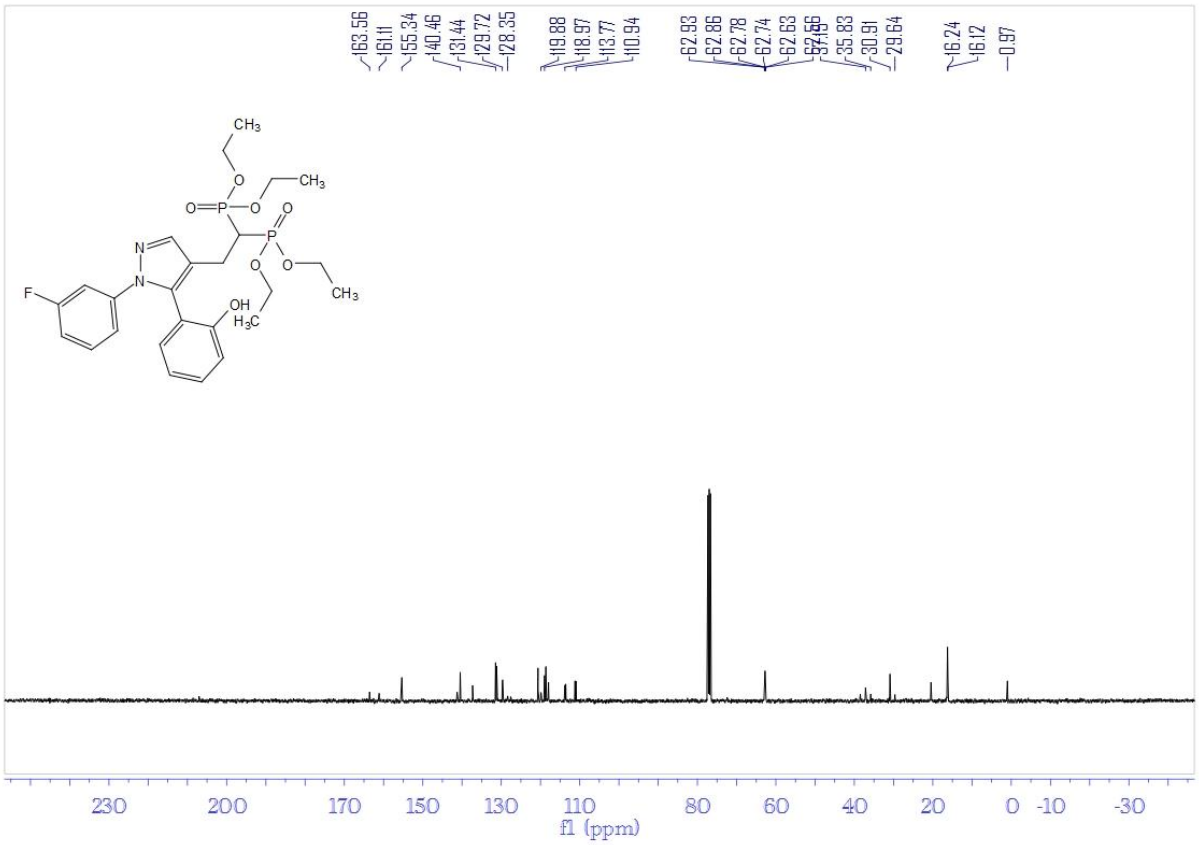
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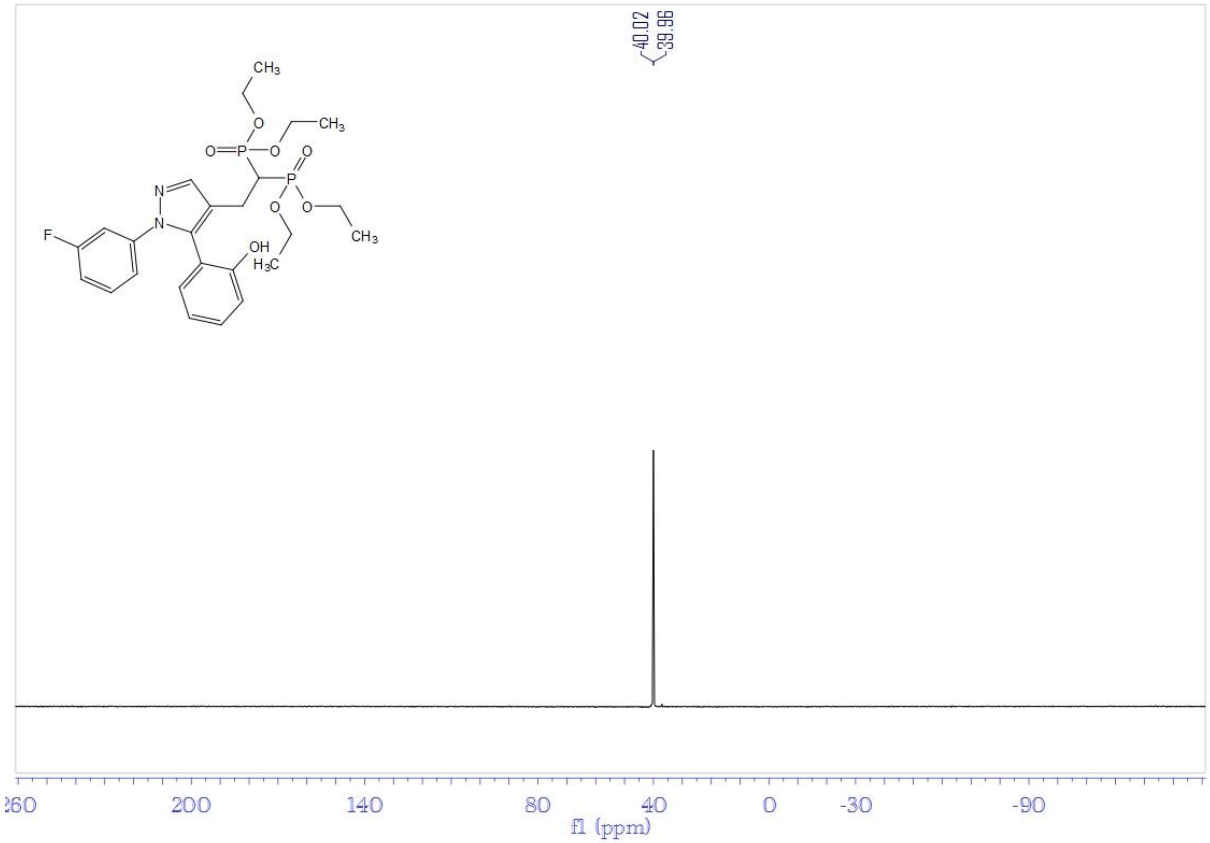
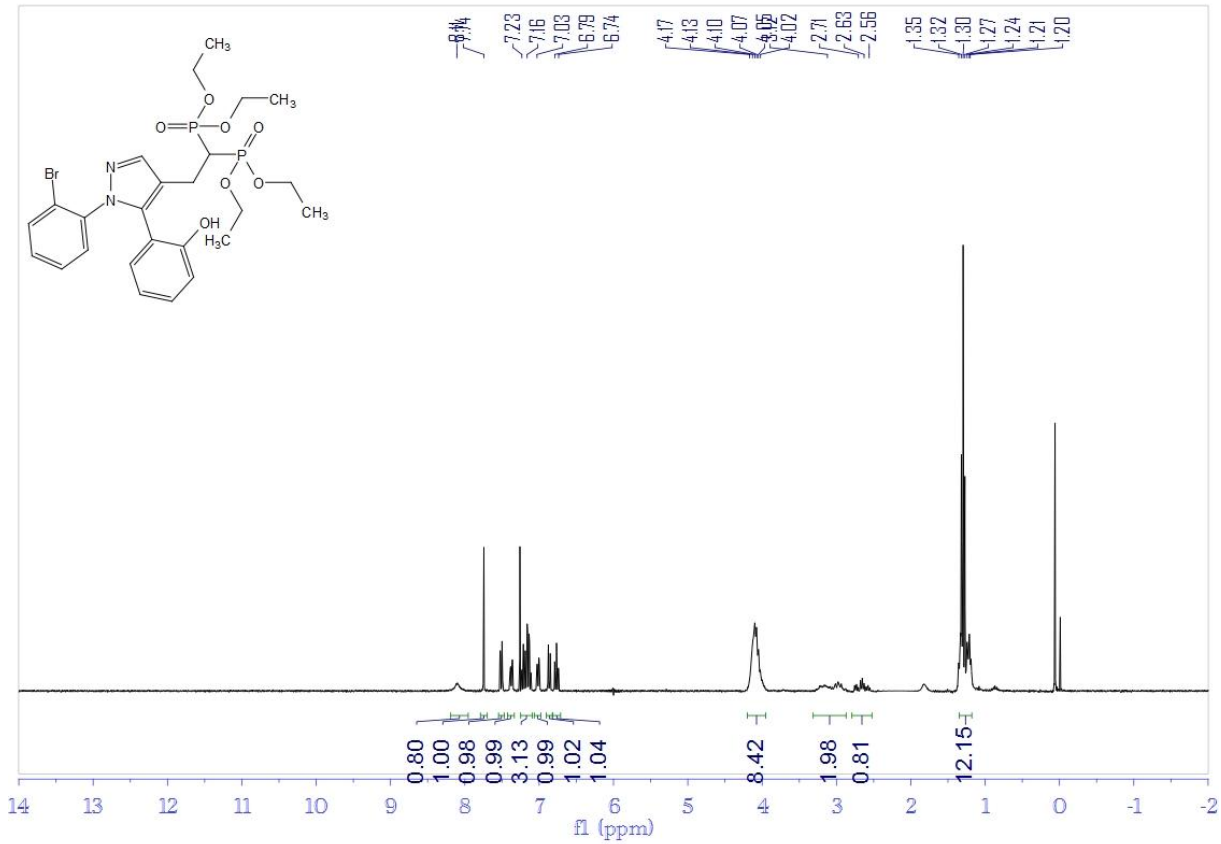
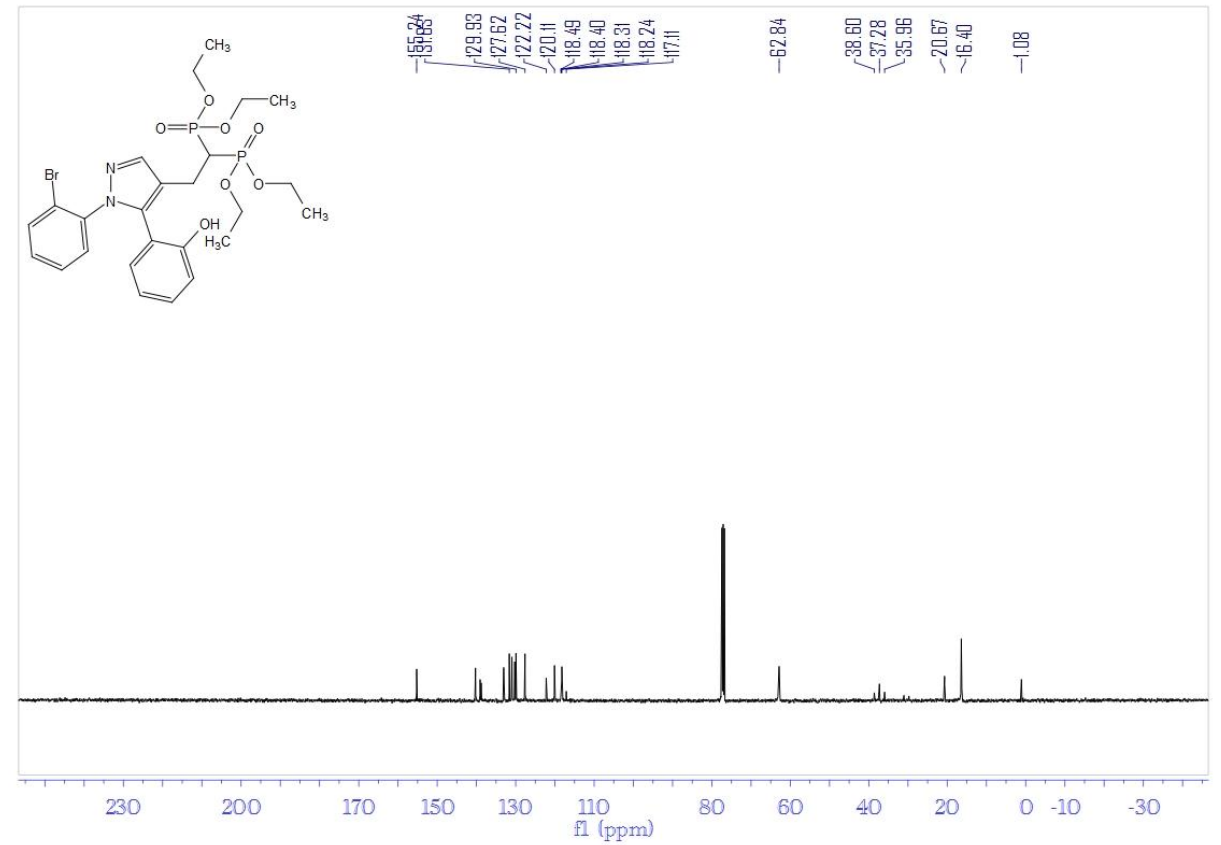
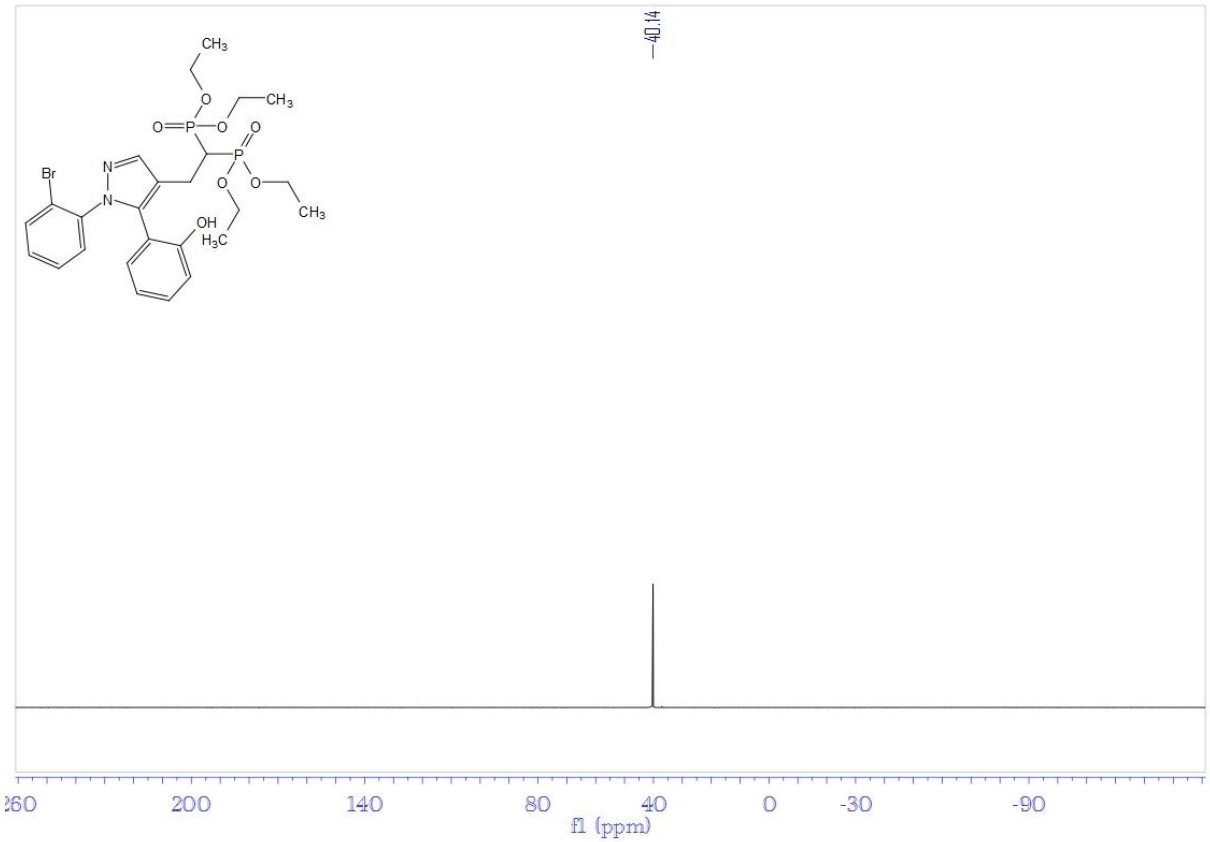
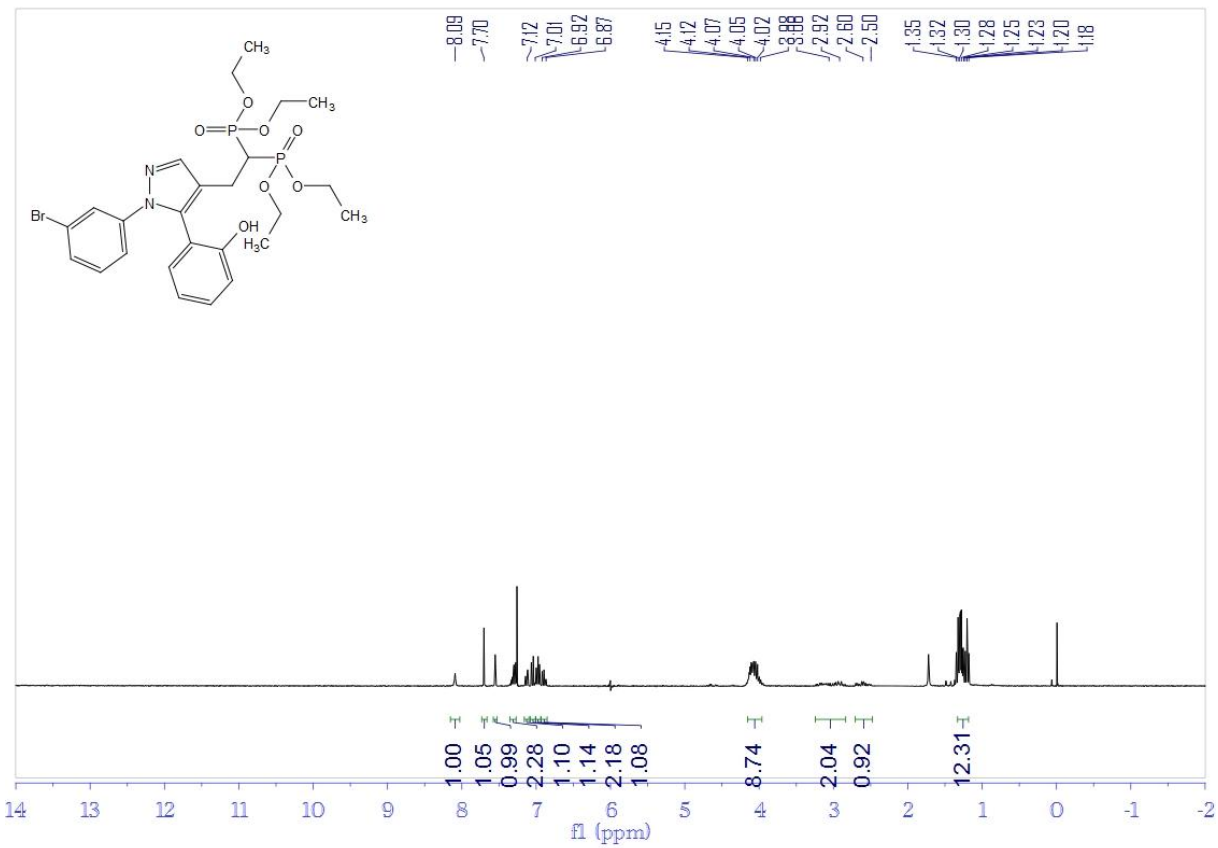
161.11
155.34
140.46
131.44
129.72
128.35
119.88
118.97
113.77
110.94
62.93
62.86
62.78
62.74
62.63
35.83
30.91
29.64
16.24
16.12
0.97
CH3
O
CH3
O=P
O
P
O
N
N
O
O
CH3
F
OH
H3C
230
200
170
150
130
110
80
60
40
20
0
-10
-30
f1 (ppm)


40.02
39.96
CH3
O
CH3
O=P
O
P
O
N
N
O
O
CH3
F
OH
H3C
260
200
140
80
40
0
-30
-90
f1 (ppm)






40.14
f1 (ppm)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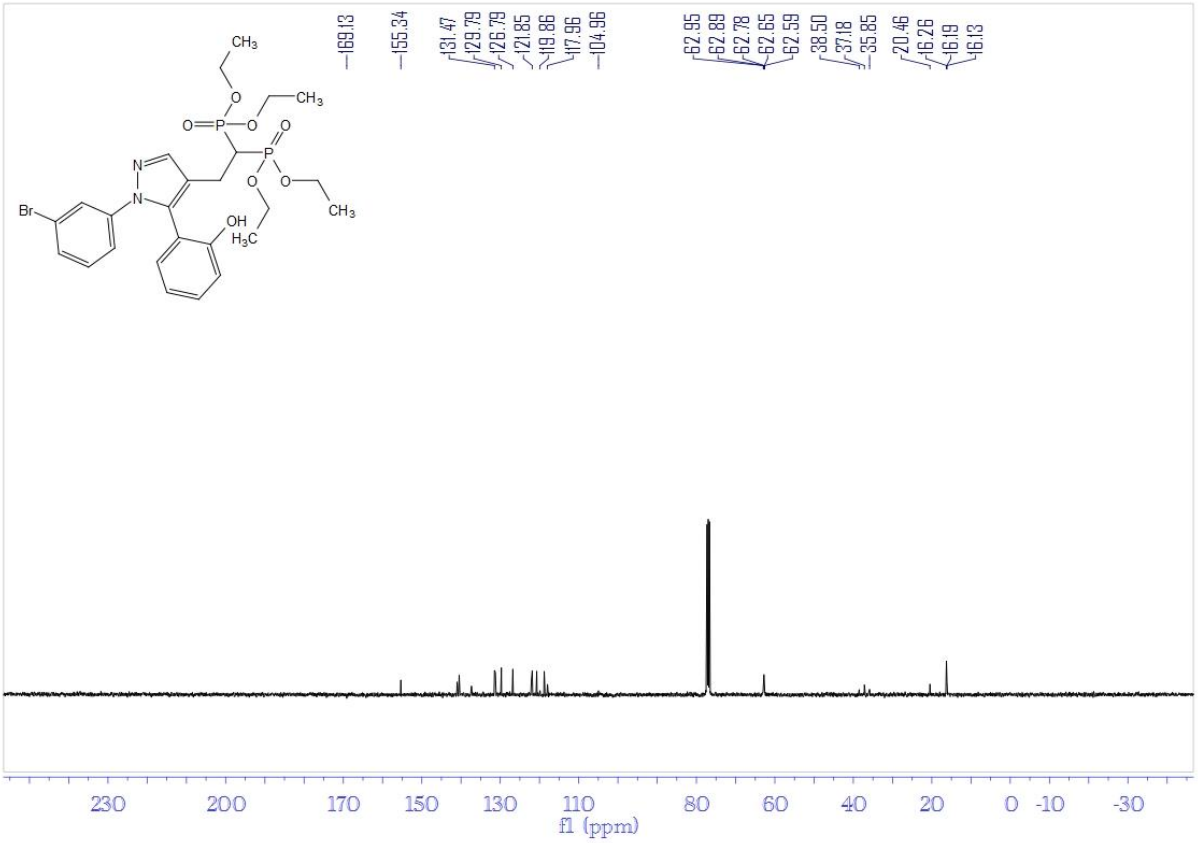
7.70
7.12
7.01
6.92
6.87
4.15
4.12
4.07
4.05
4.02
2.92
2.60
2.50
1.35
1.32
1.30
1.28
1.25
1.23
1.20
1.18
1.00
1.05
0.99
2.28
1.10
1.14
2.18
1.08
8.74
2.04
0.92
12.31
f1 (ppm)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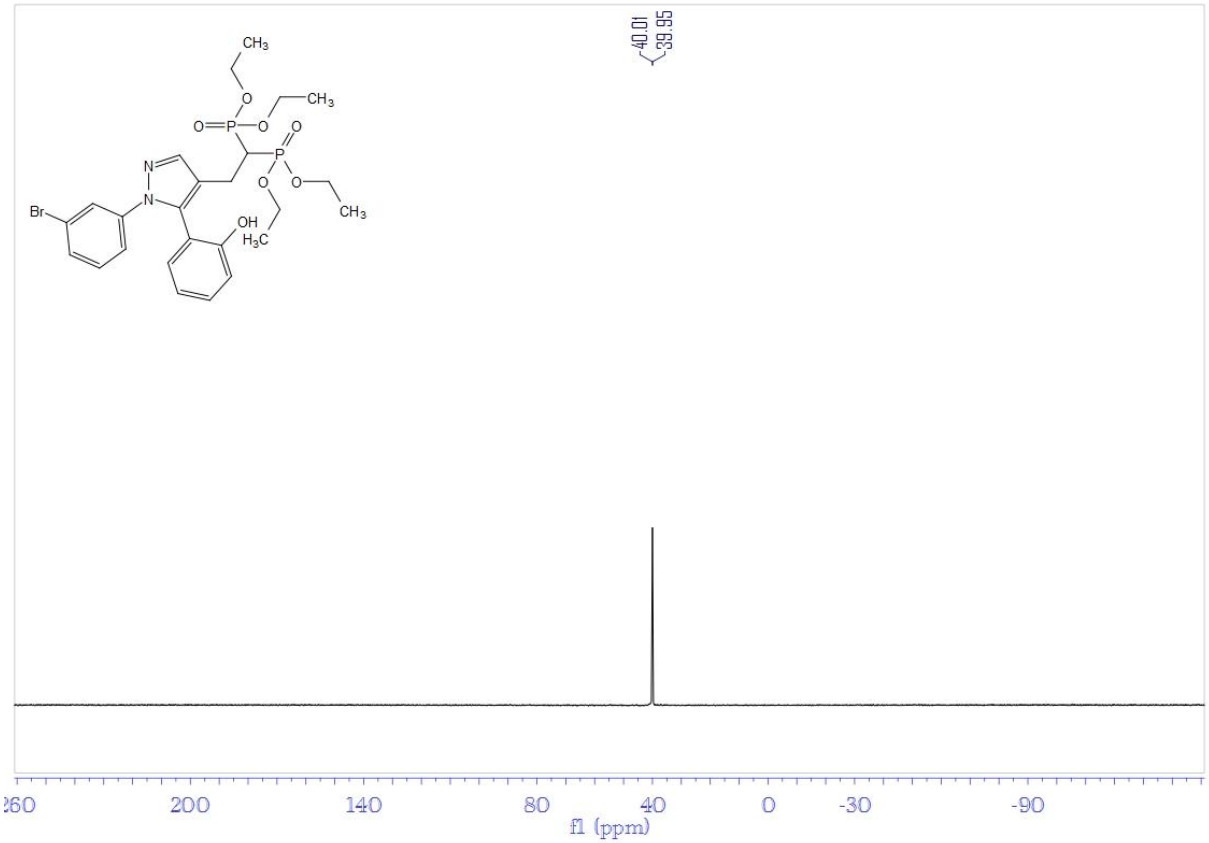
129.79
126.79
121.85
119.86
117.96
104.96
62.95
62.89
62.78
62.65
62.59
38.50
37.18
35.85
20.46
16.26
16.19
16.13
CH3
O
CH3
O=P—O
O
P
N
N
Br
OH
H3C
O
P
O
O
CH3
230
200
170
150
130
110
80
60
40
20
0
-10
-30
f1 (ppm)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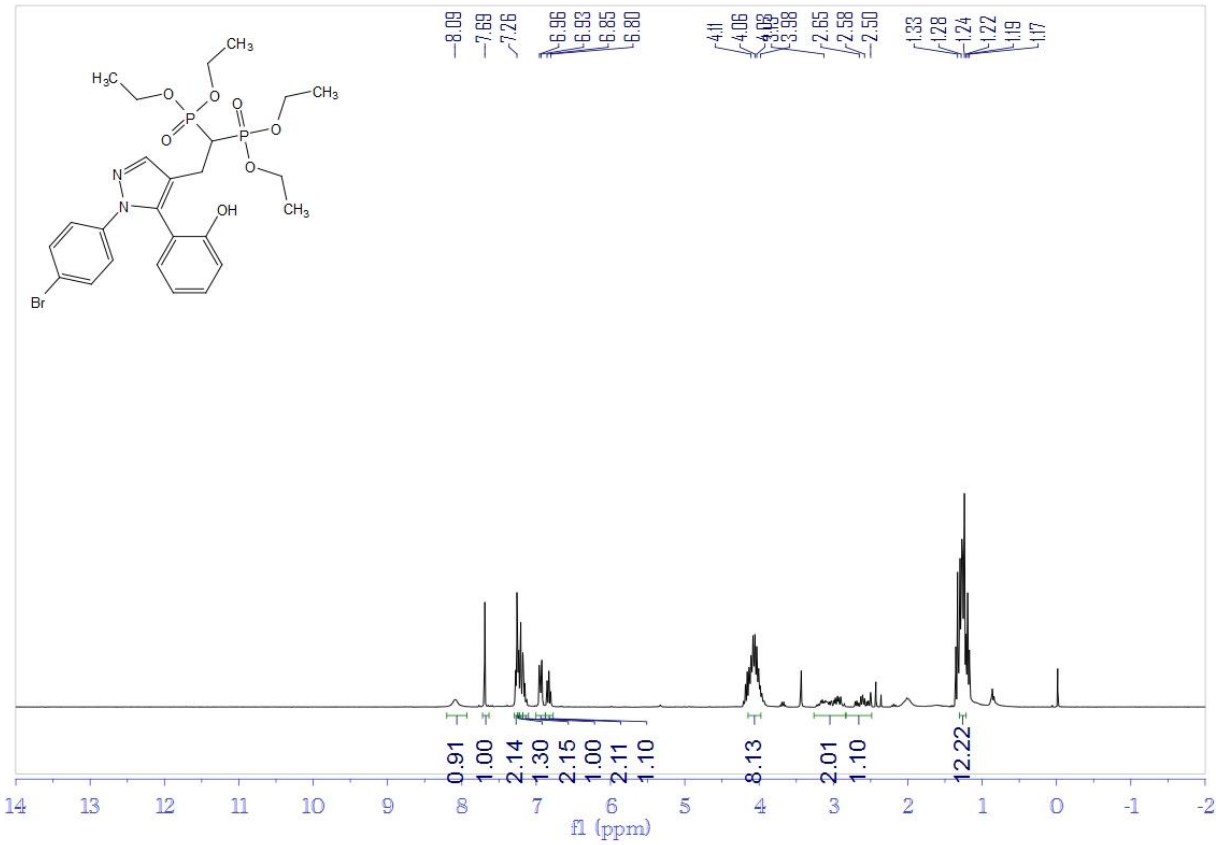
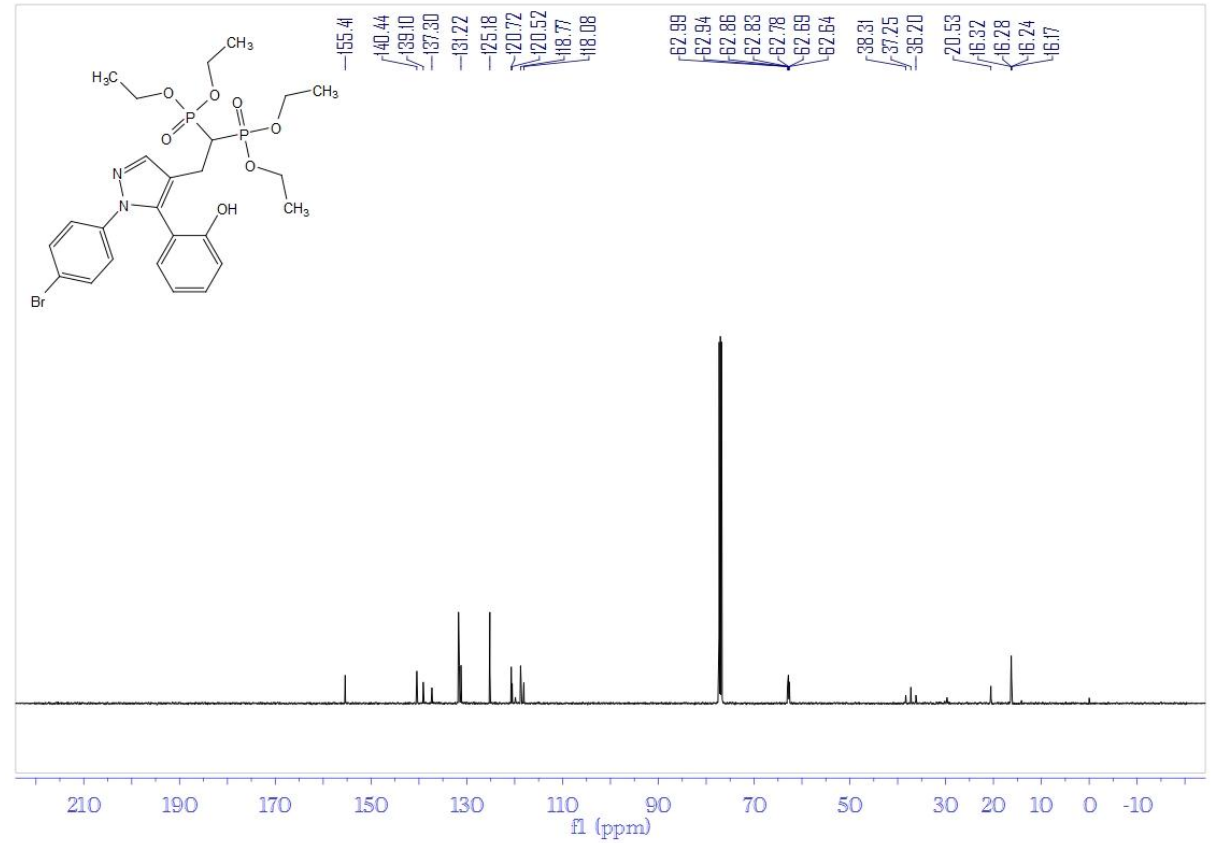
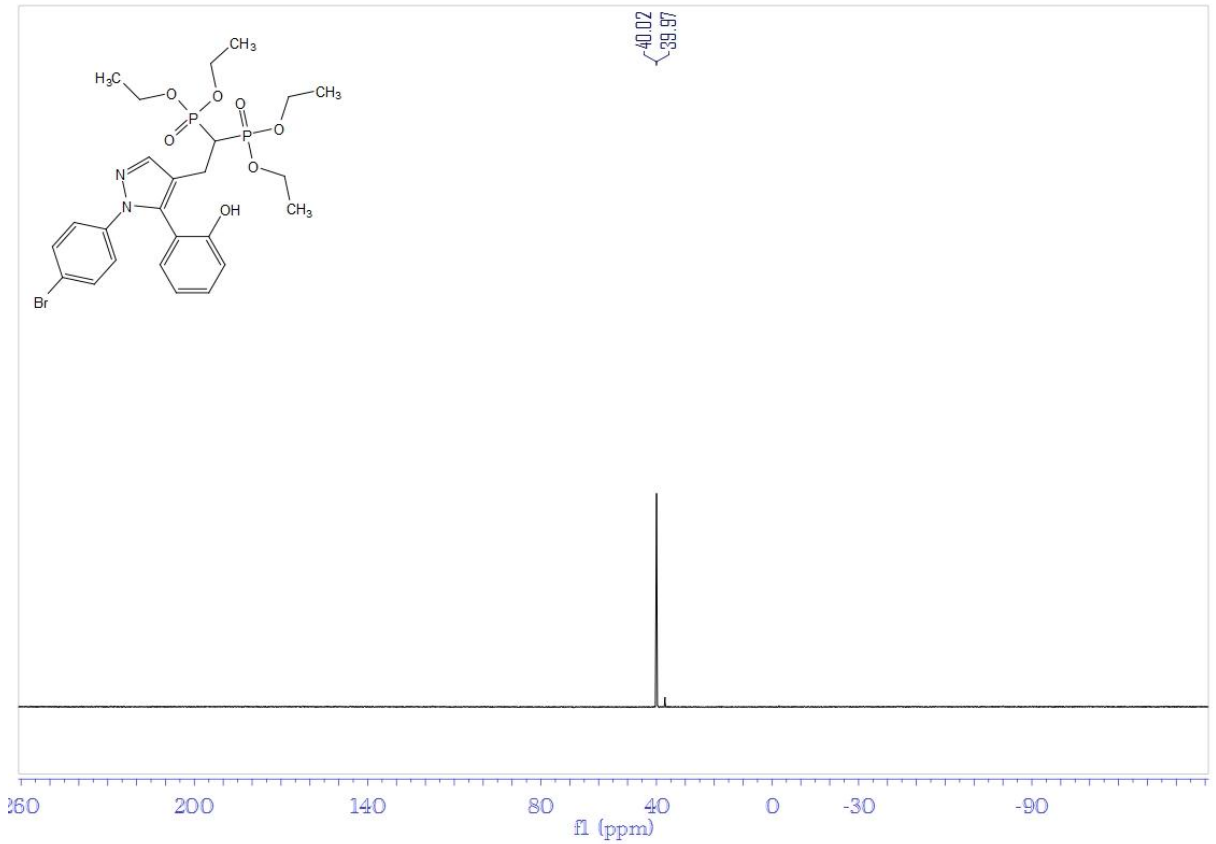
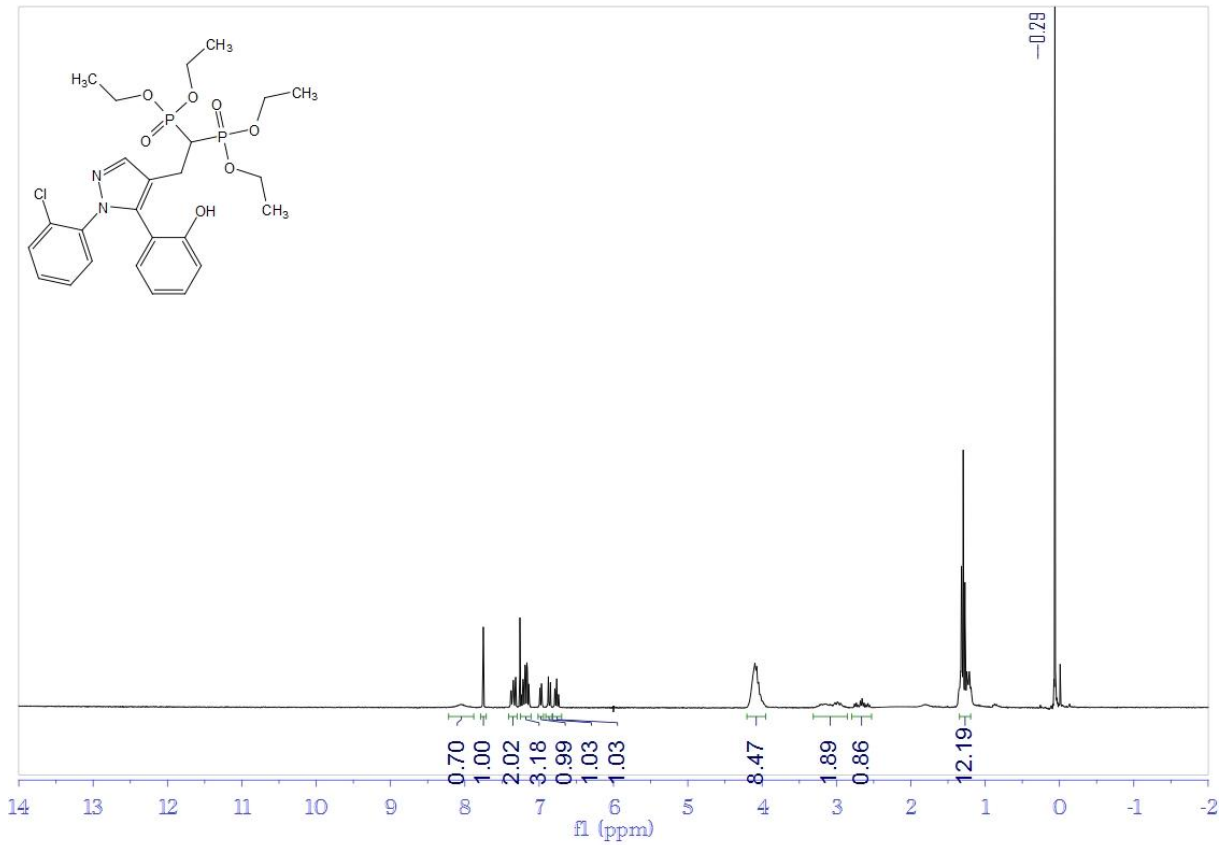
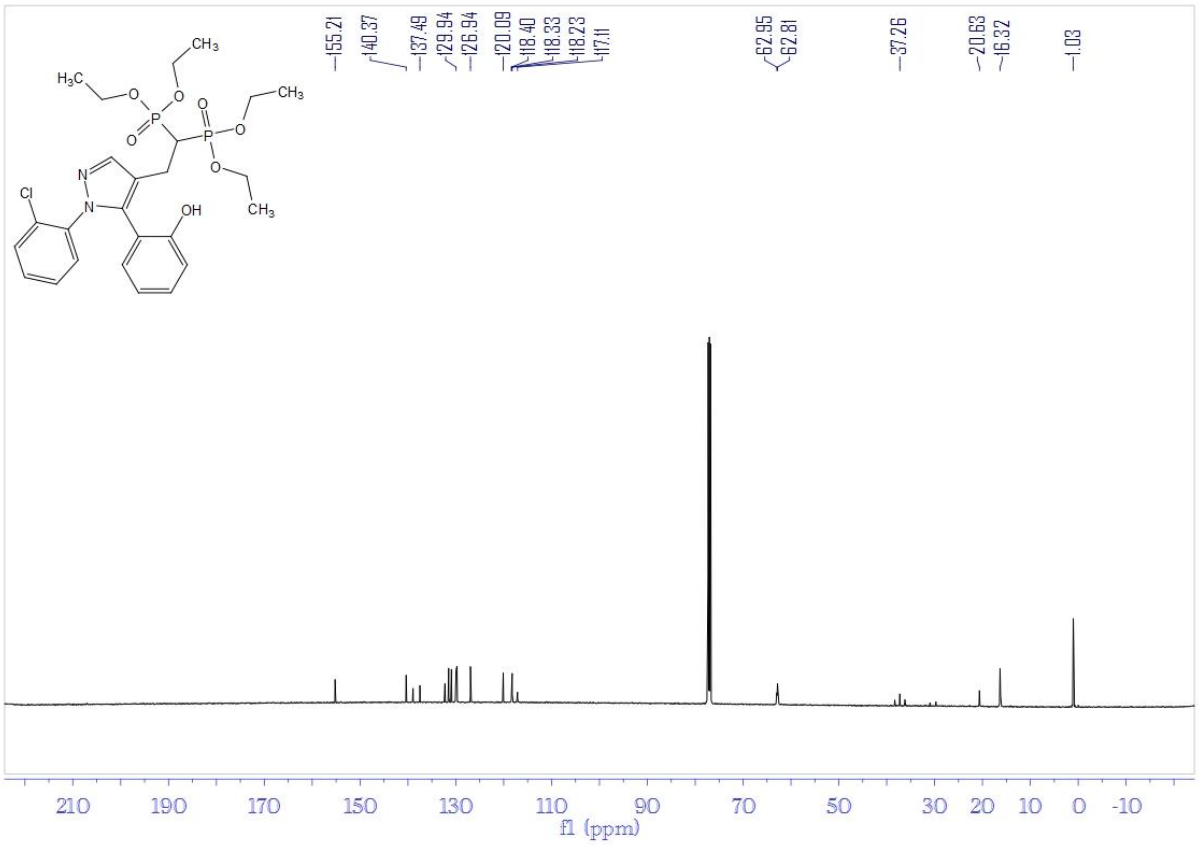
39.95
CH3
O
CH3
O=P—O
O
P
N
N
Br
OH
H3C
O
P
O
O
CH3
260
200
140
80
40
0
-30
-90
f1 (ppm)


8.09
7.69
7.26
6.96
6.93
6.85
6.80
4.11
4.06
4.03
3.98
2.65
2.58
2.50
1.33
1.28
1.24
1.22
1.19
1.17
0.91
1.00
2.14
1.30
2.15
1.00
2.11
1.10
8.13
2.01
1.10
12.22
f1 (ppm)


155.44
140.44
139.10
137.30
131.22
125.18
120.72
120.52
118.77
118.08
62.99
62.94
62.86
62.83
62.78
62.69
62.64
38.31
37.25
36.20
20.53
16.32
16.28
16.24
16.17
f1 (ppm)



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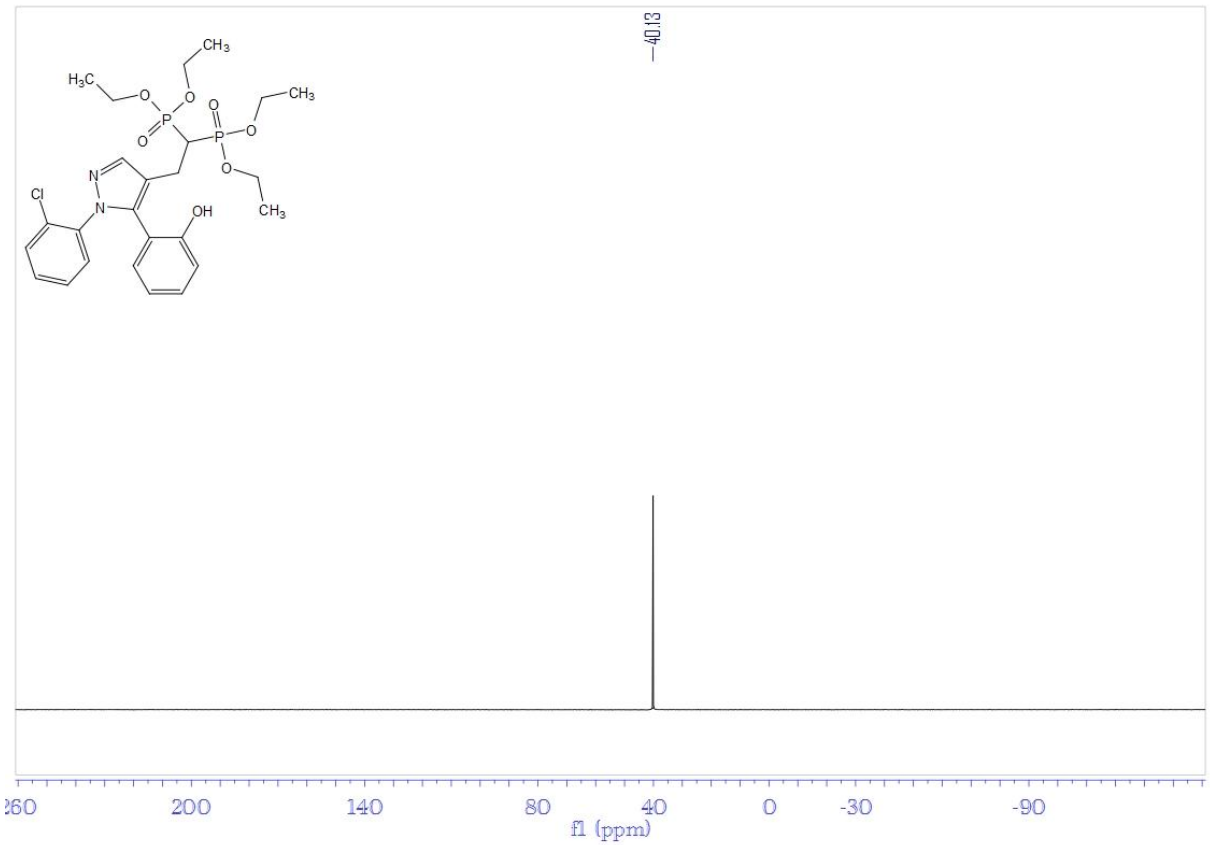
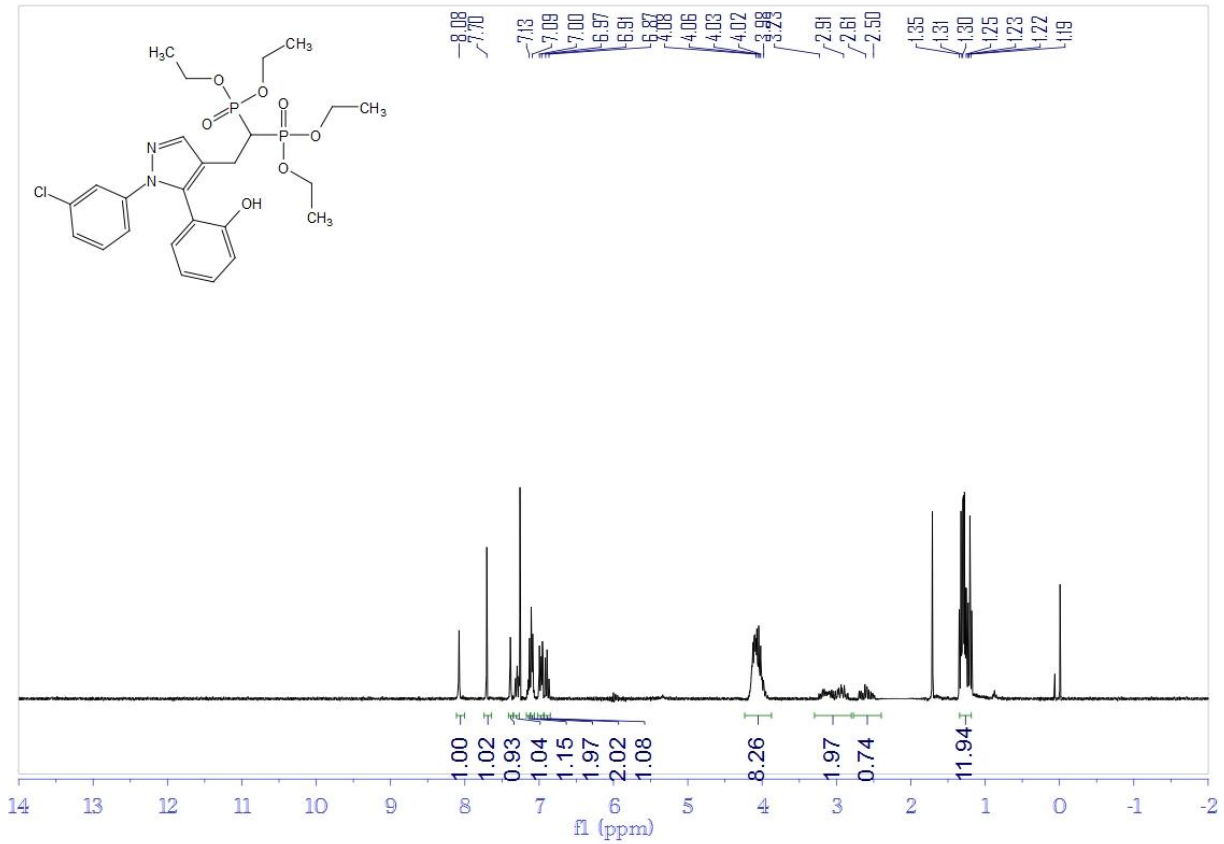
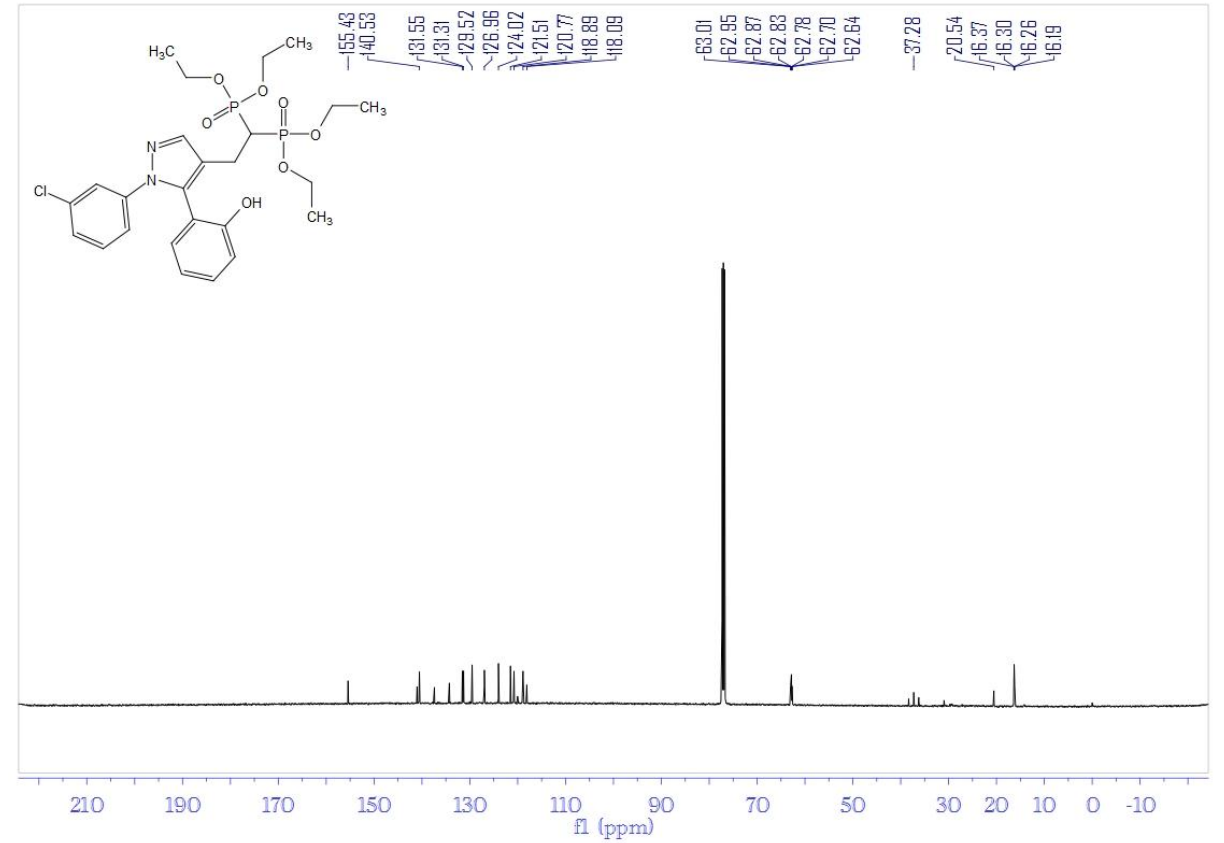
140.37
137.49
129.94
126.94
120.09
118.40
118.33
118.23
117.11
62.95
62.81
37.26
20.63
16.32
1.03
CH3
H3C
O
P
O
CH3
N
N
Cl
OH
210
190
170
150
130
110
90
70
50
30
20
10
0
-10
f1 (ppm)


40.13
CH3
H3C
O
P
O
CH3
N
N
Cl
OH
260
200
140
80
40
0
-30
-90
f1 (ppm)


8.08
7.70
7.13
7.09
7.00
6.97
6.91
6.87
4.08
4.06
4.03
4.02
3.98
3.23
2.91
2.61
2.50
1.35
1.31
1.30
1.25
1.23
1.22
1.19
1.00
1.02
0.93
1.04
1.15
1.97
2.02
1.08
8.26
1.97
0.74
11.94
f1 (ppm)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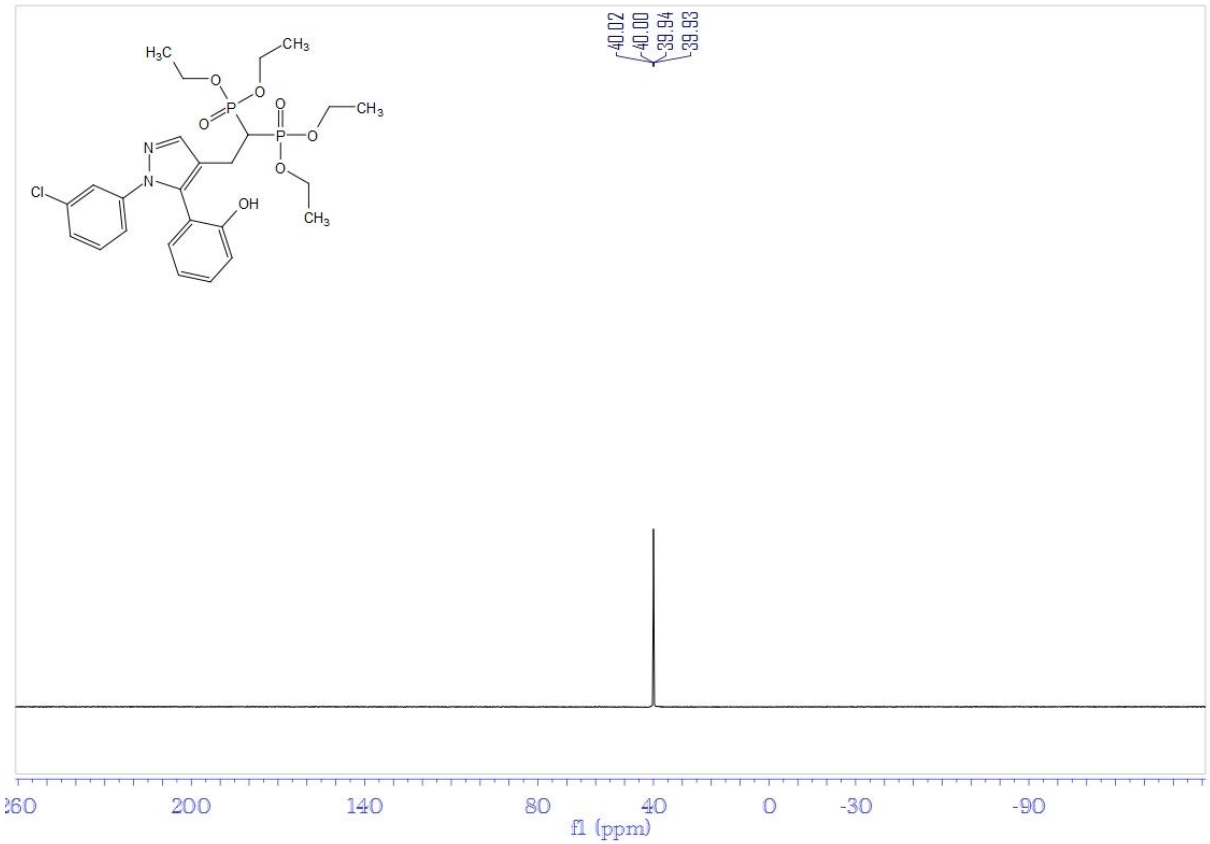
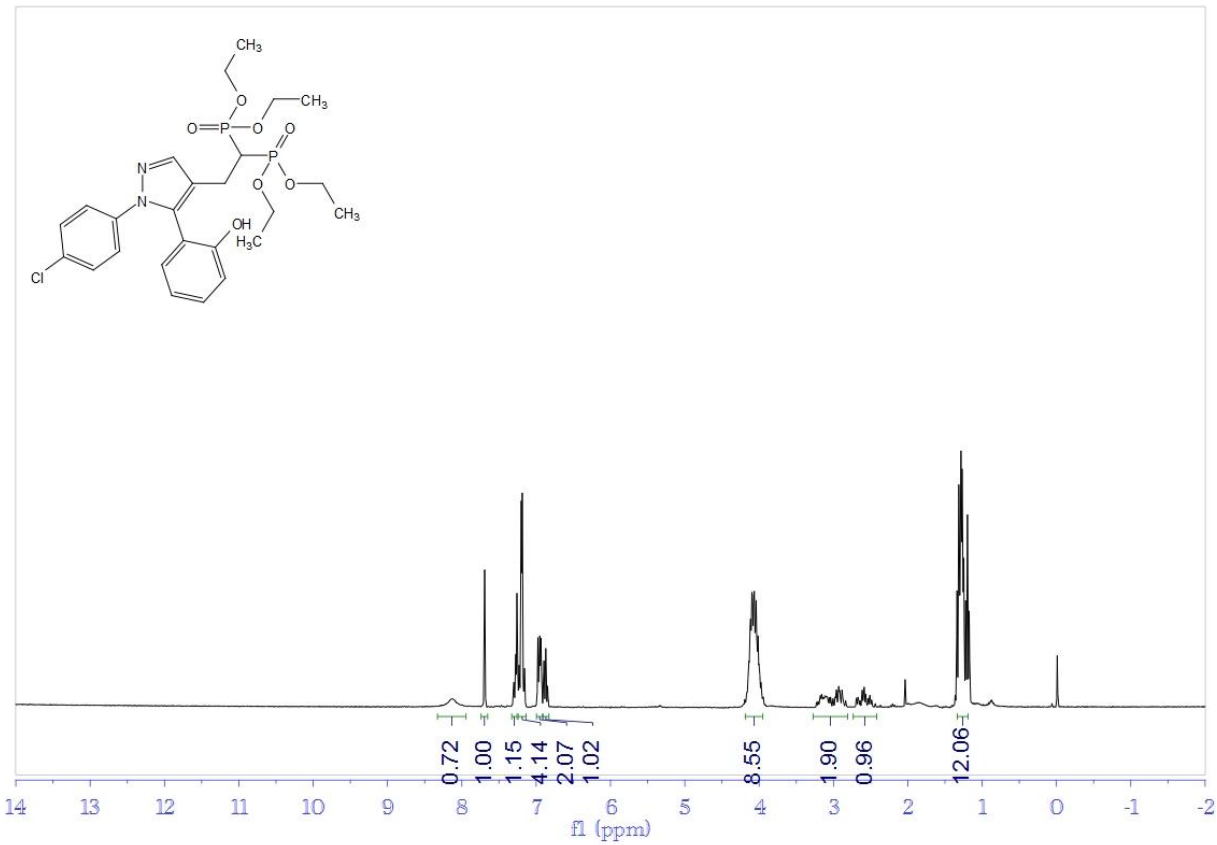
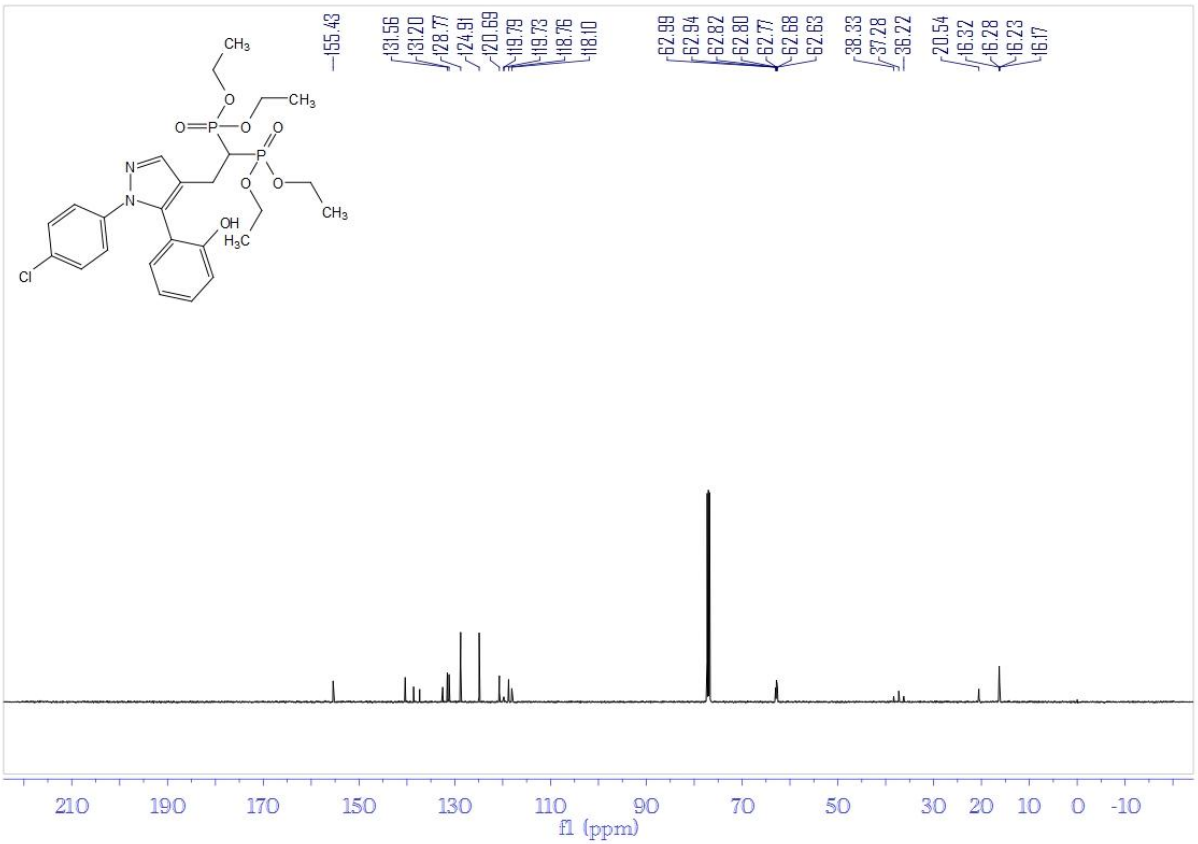
140.53
131.55
131.31
129.52
126.96
124.02
121.51
120.77
118.89
118.09
63.01
62.95
62.87
62.83
62.78
62.70
62.64
37.28
20.54
16.37
16.30
16.26
16.19
f1 (ppm)



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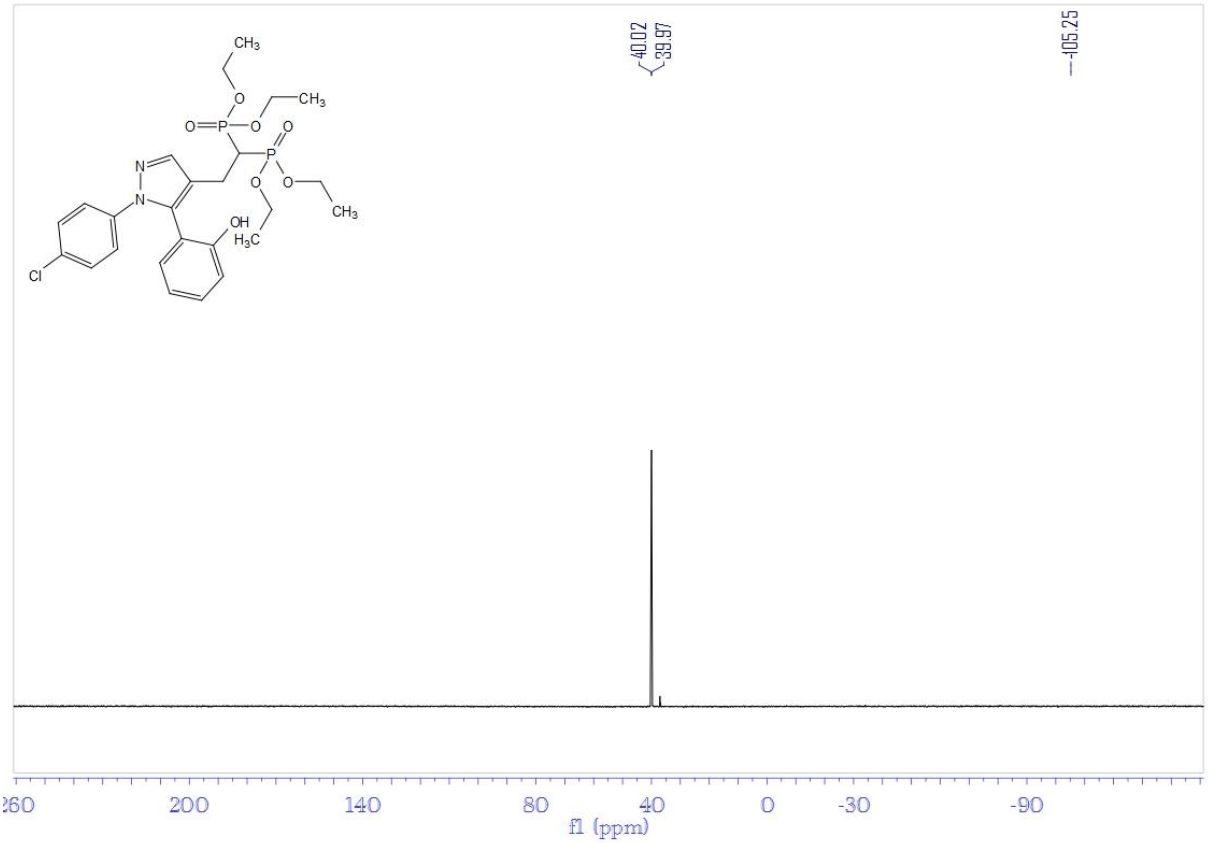
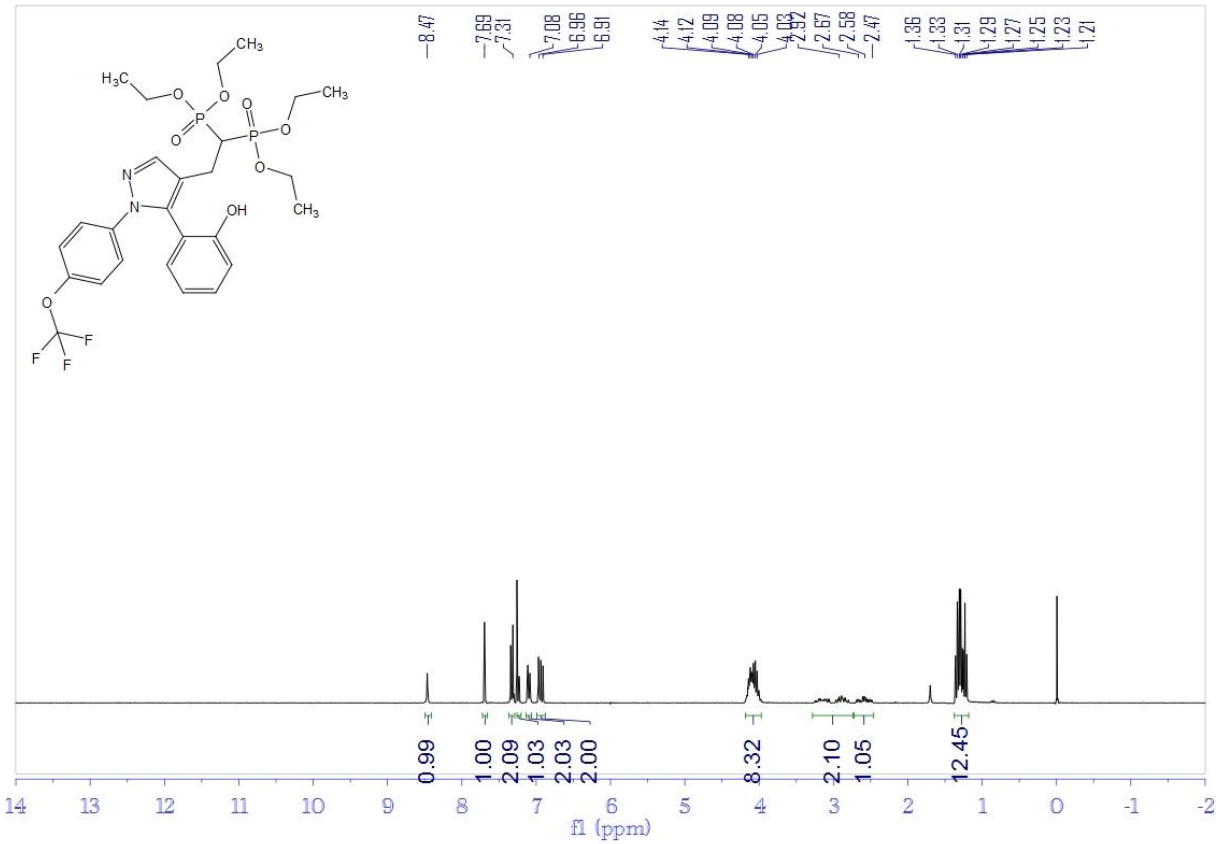
131.56
131.20
128.77
124.91
120.69
119.79
119.73
118.76
118.10
62.99
62.94
62.82
62.80
62.77
62.68
62.63
38.33
37.28
36.22
20.54
16.32
16.28
16.23
16.17
CH3
O
CH3
O=P—O
O
P
N
N
O
O
CH3
OH
H3C
Cl
210
190
170
150
130
110
90
70
50
30
20
10
0
-10
f1 (ppm)


40.02
39.97
-105.25
CH3
O
CH3
O=P—O
O
P
N
N
O
O
CH3
OH
H3C
Cl
260
200
140
80
40
0
-30
-90
f1 (ppm)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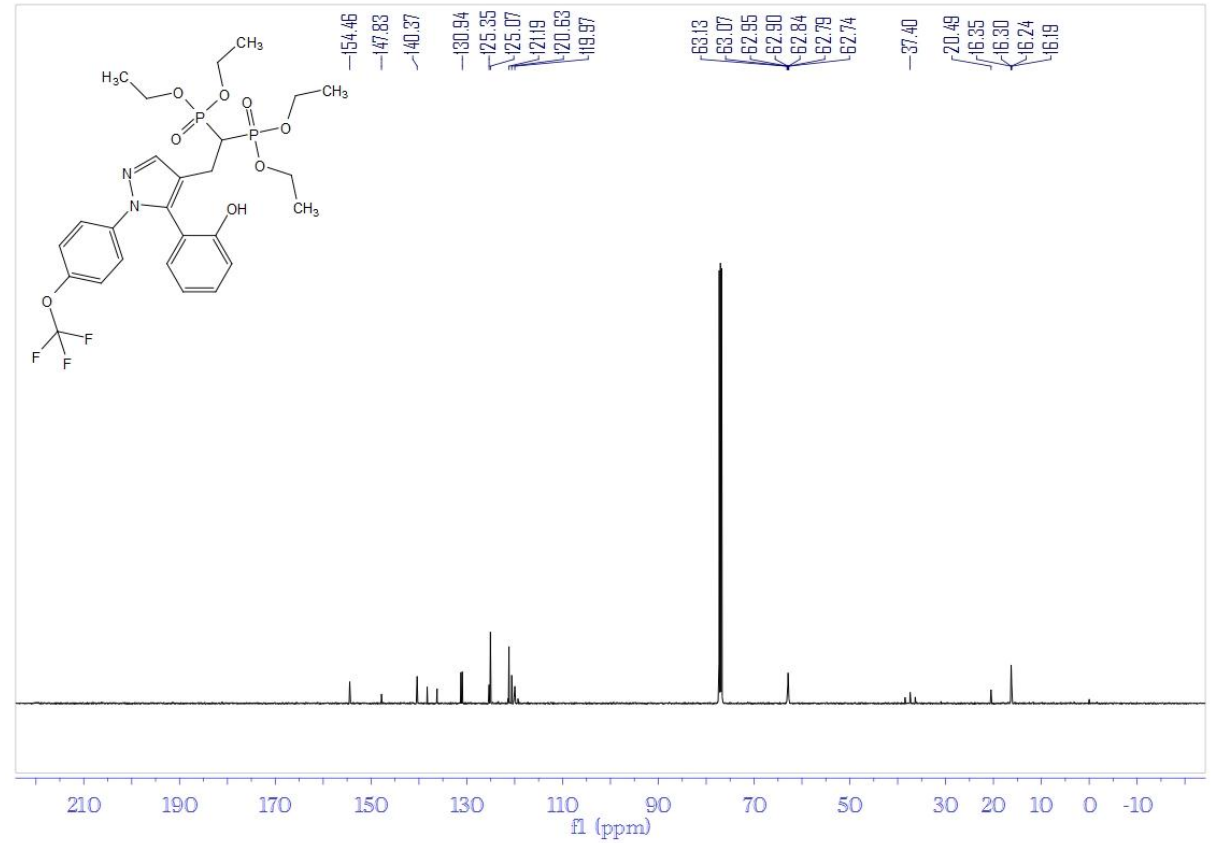
7.69
7.31
7.08
6.96
6.91
4.14
4.12
4.09
4.08
4.05
2.67
2.58
2.47
1.36
1.33
1.31
1.29
1.27
1.25
1.23
1.21
0.99
1.00
2.09
1.03
2.03
2.00
8.32
2.10
1.05
12.45
f1 (ppm)


154.46
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130.94
125.35
125.07
121.19
120.63
119.97
63.13
63.07
62.95
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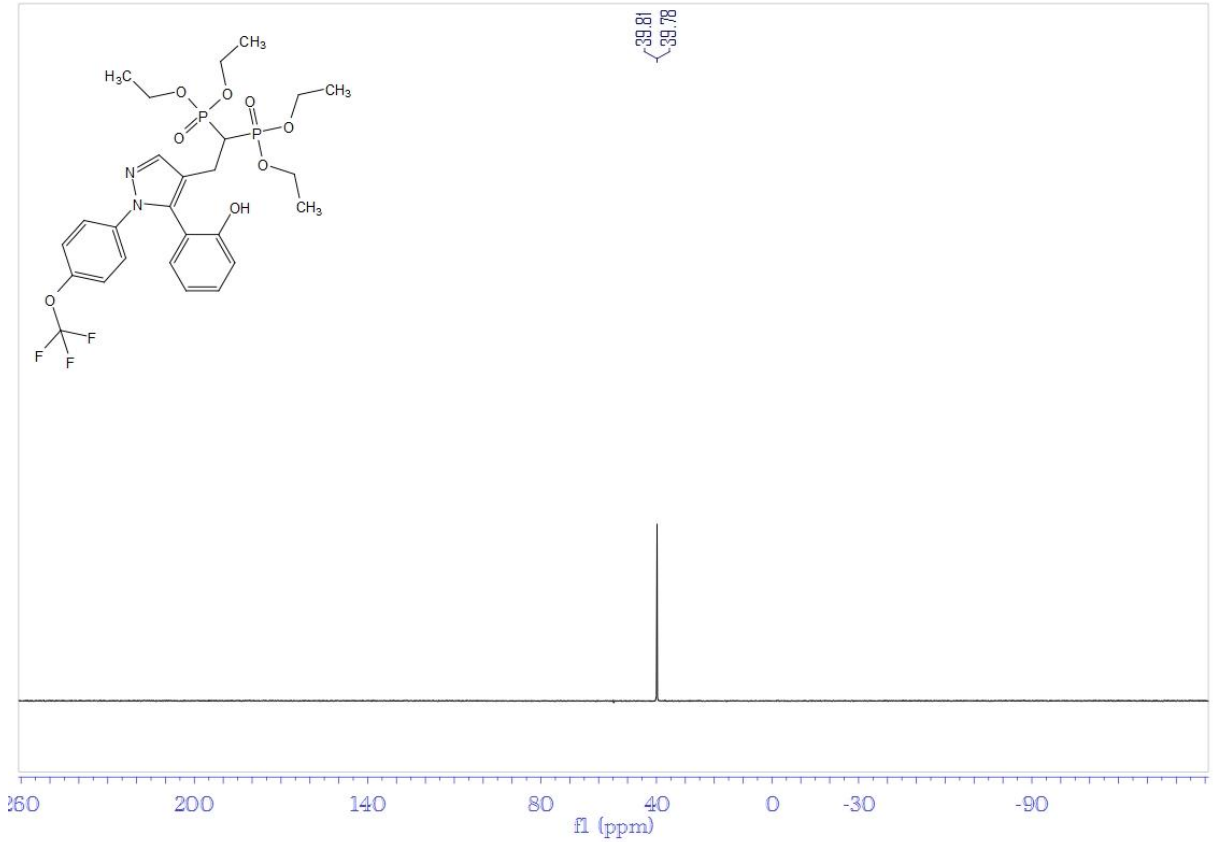
16.35
16.30
16.24
16.19
f1 (ppm)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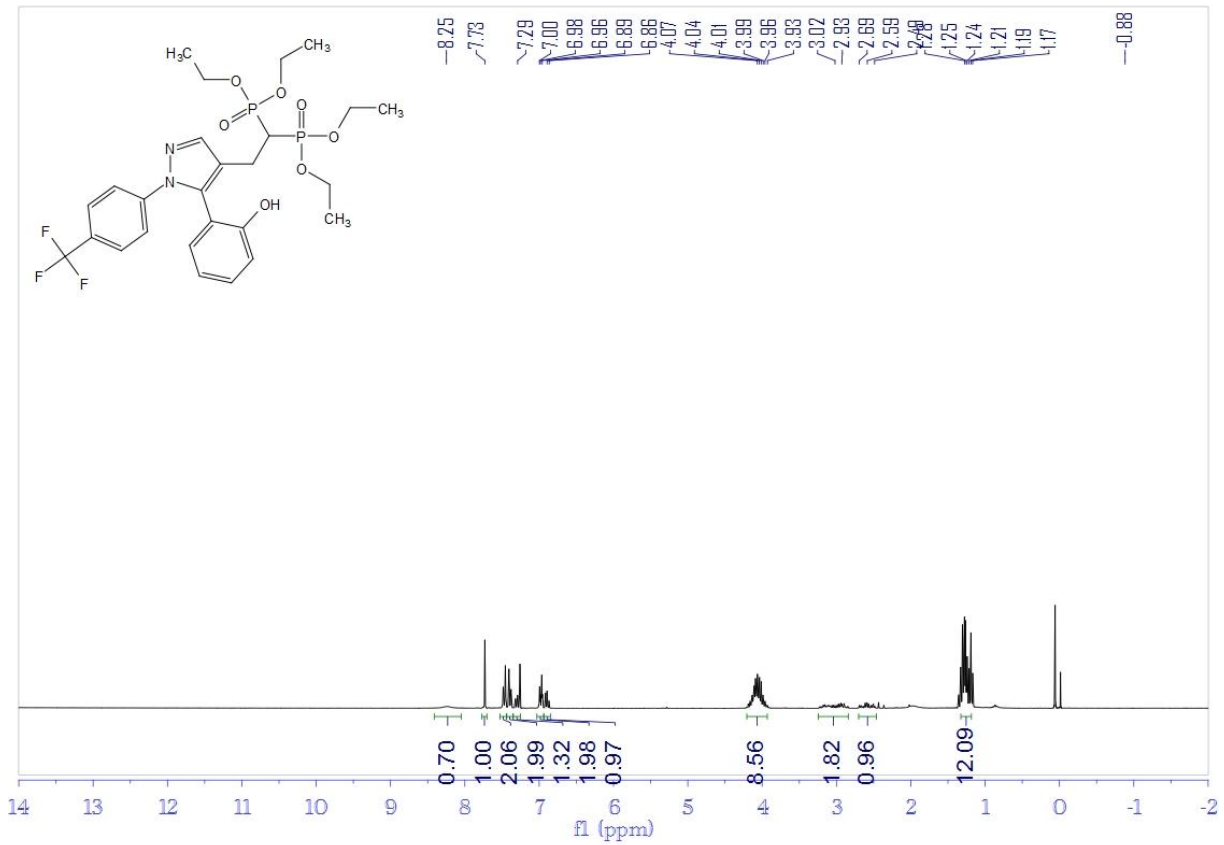
39.78
f1 (ppm)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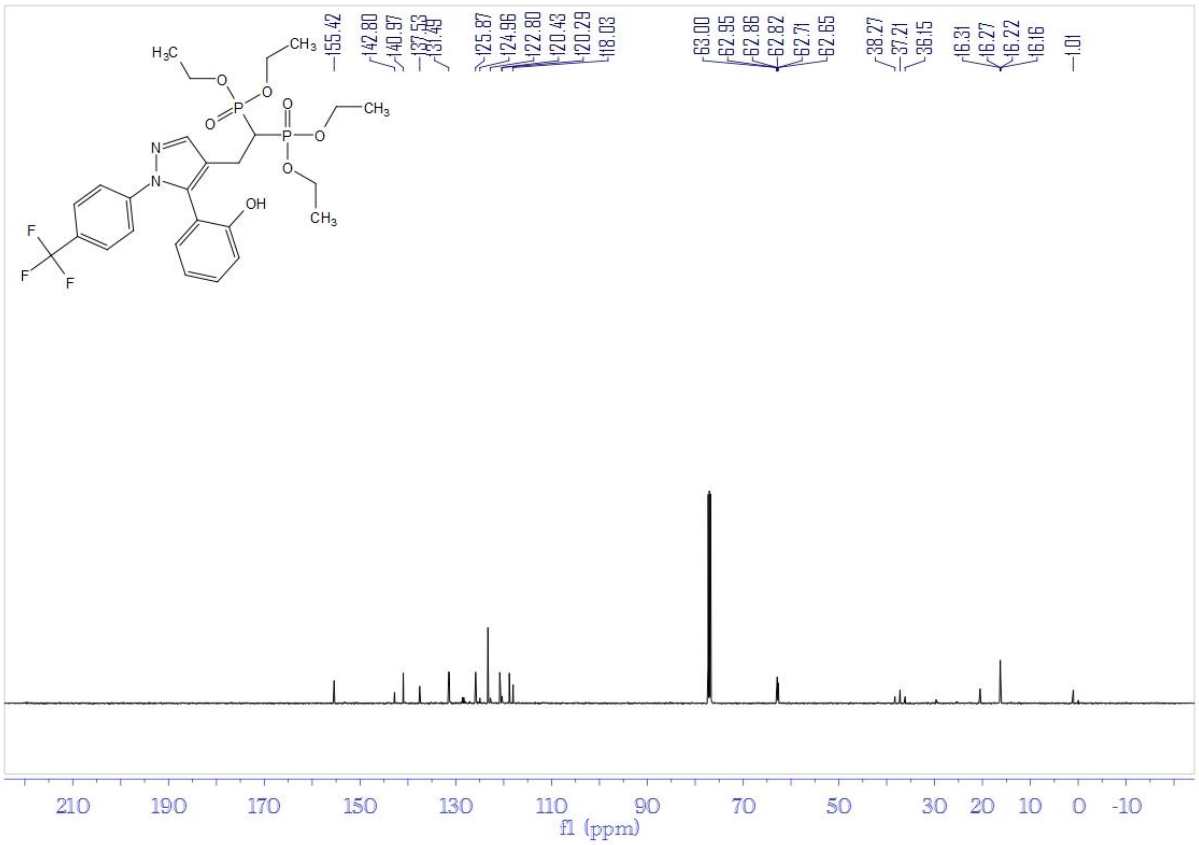
7.73
7.29
7.00
6.98
6.96
6.89
6.86
4.07
4.04
4.01
3.99
3.96
3.93
3.02
2.93
2.69
2.59
1.25
1.24
1.21
1.19
1.17
0.88
0.70
1.00
2.06
1.99
1.32
1.98
0.97
8.56
1.82
0.96
12.09
f1 (ppm)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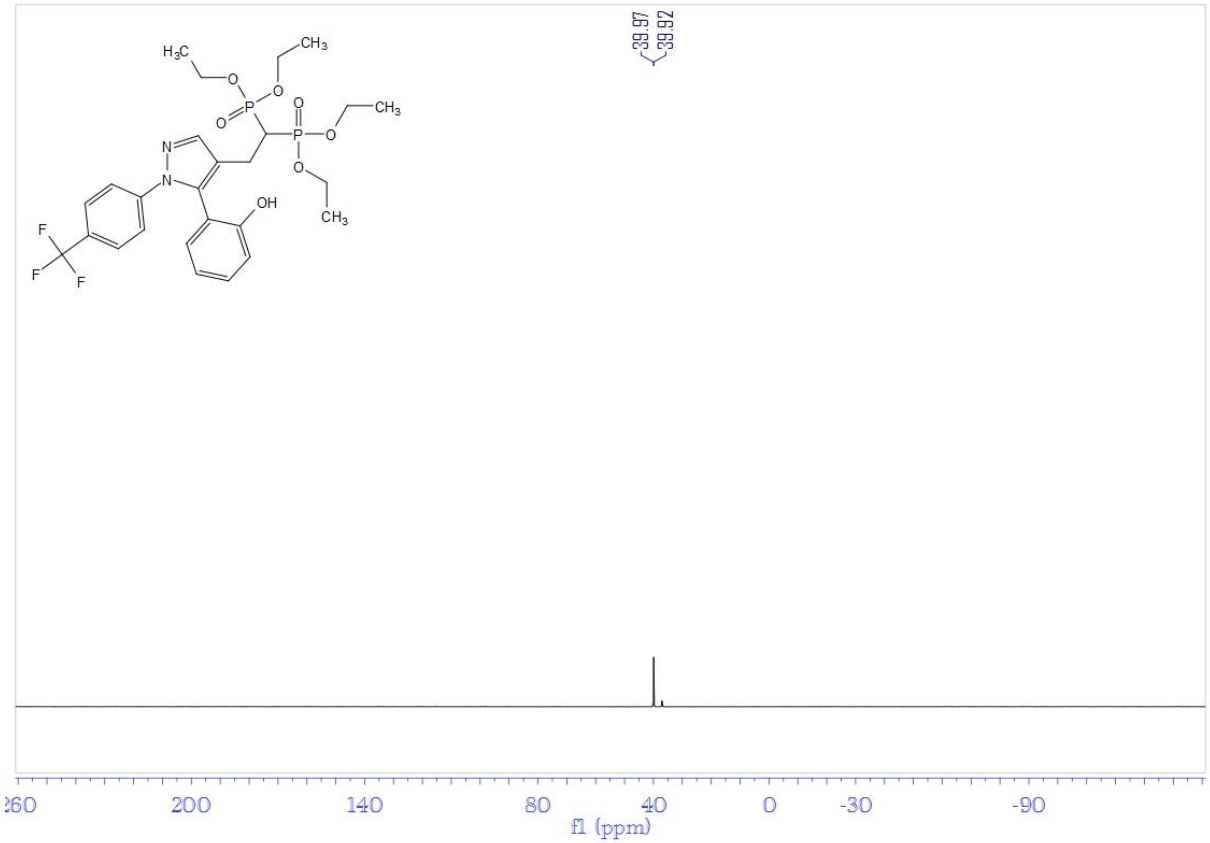
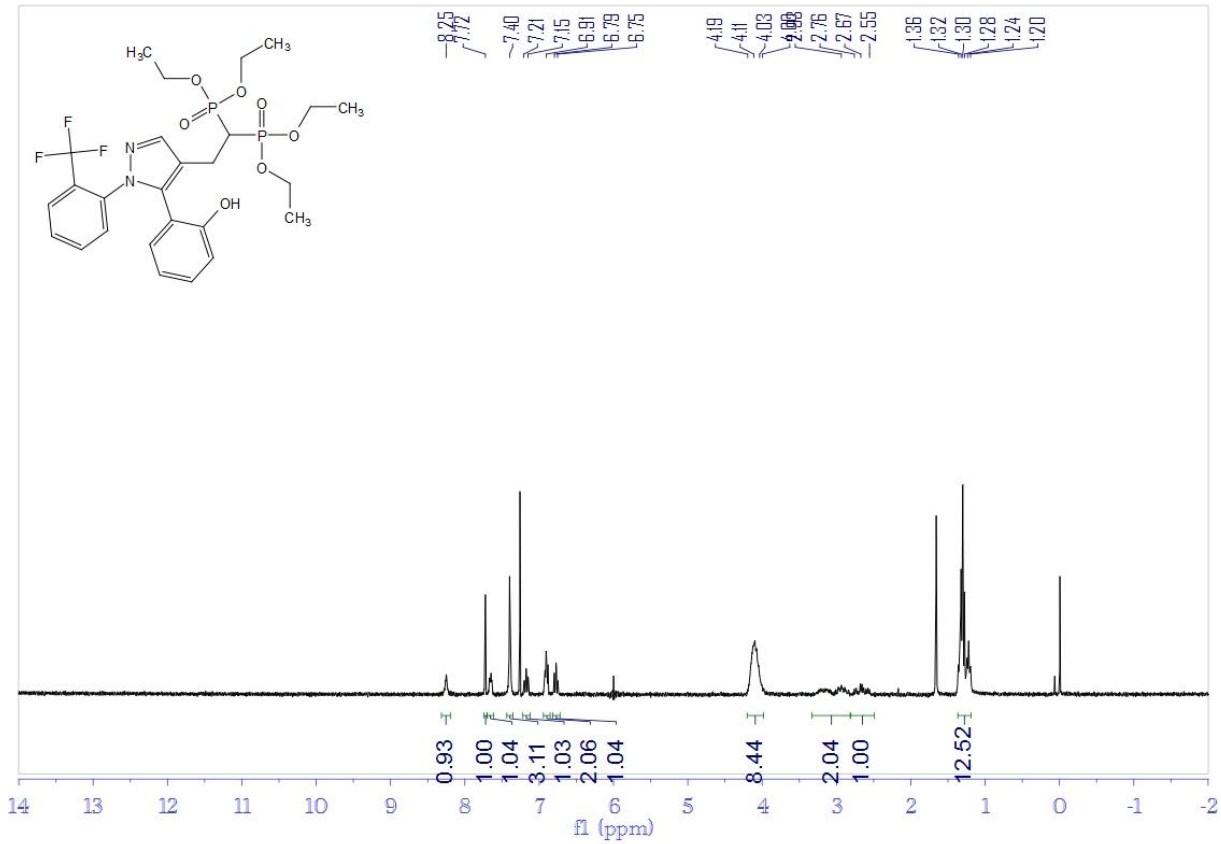
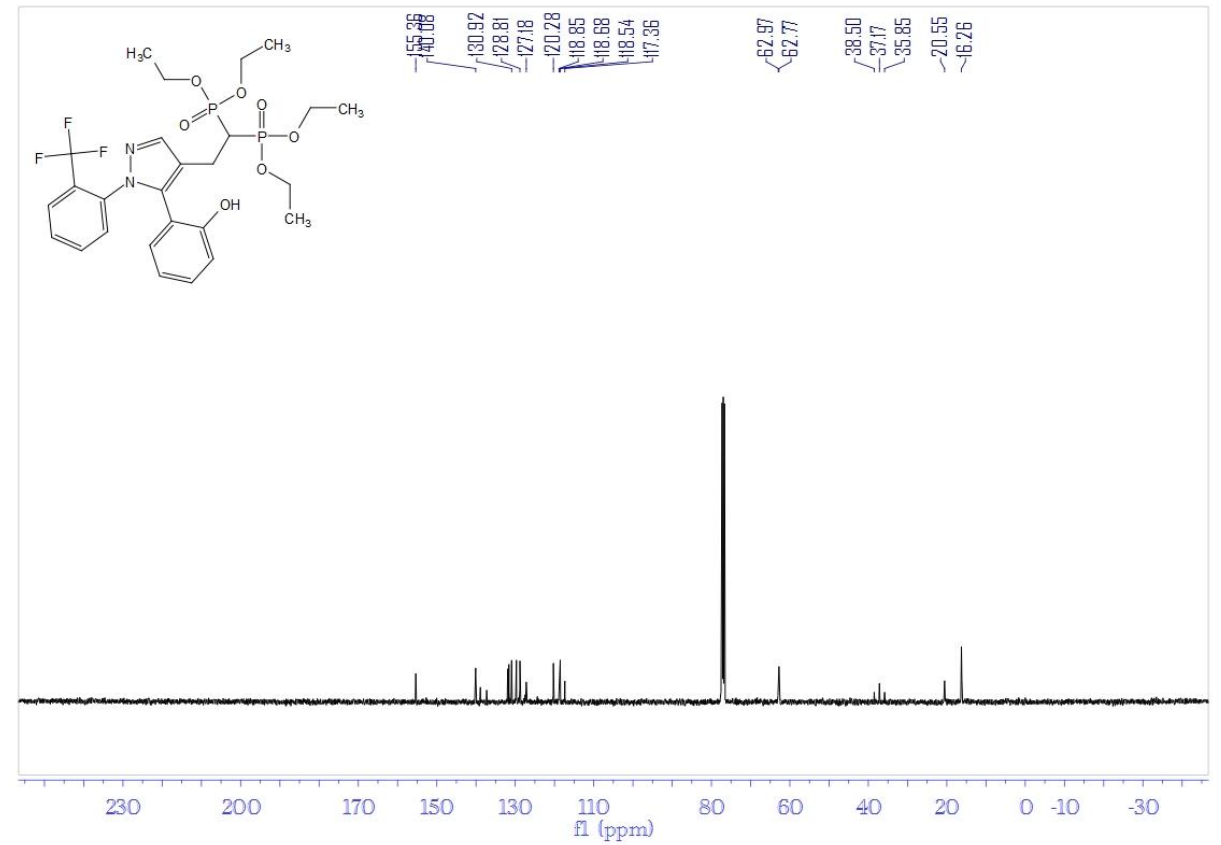
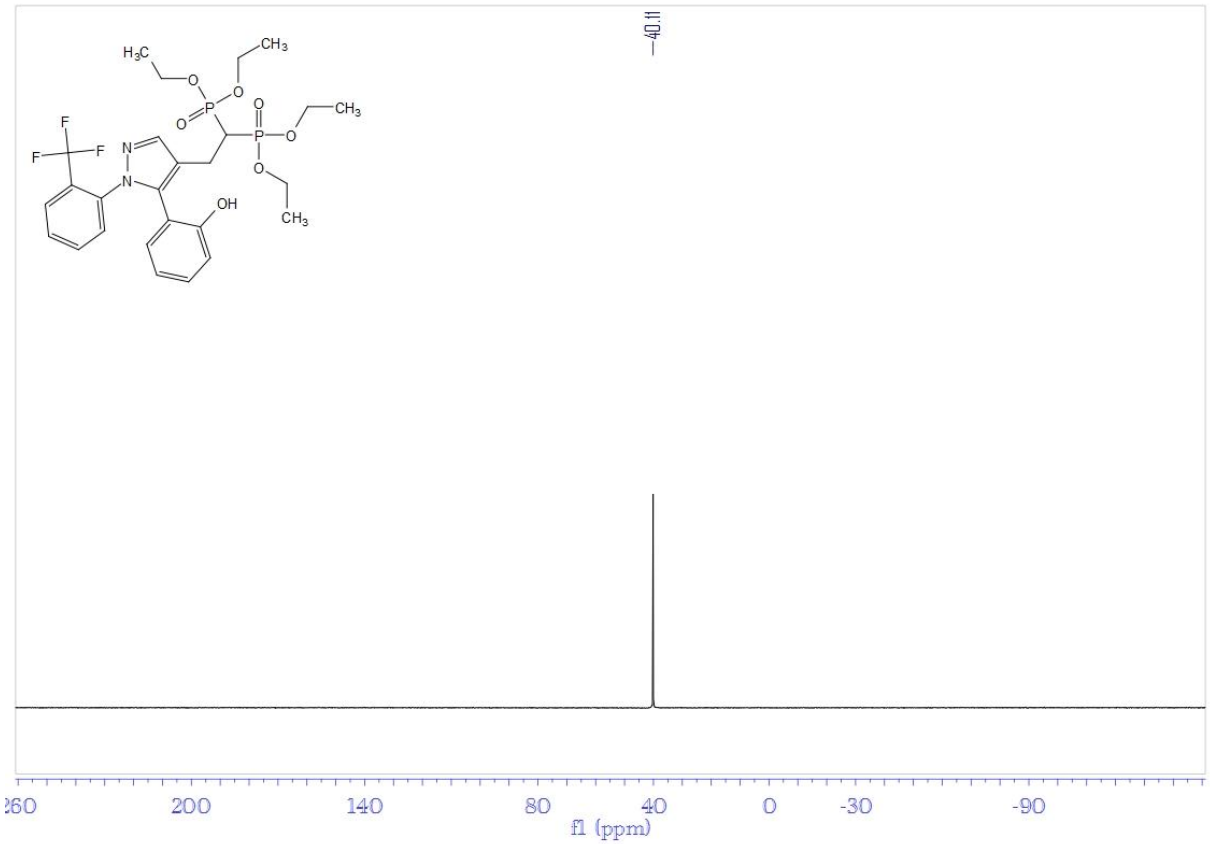
127.53
121.49
125.87
124.96
122.80
120.43
120.29
118.03
63.00
62.95
62.86
62.82
62.71
62.65
38.27
37.21
36.15
16.31
16.27
16.22
16.16
1.01
H3C
CH3
O
P
O
CH3
N
OH
F
F
F
210
190
170
150
130
110
90
70
50
30
20
10
0
-10
f1 (ppm)


39.97
39.92
H3C
CH3
O
P
O
CH3
N
OH
F
F
F
260
200
140
80
40
0
-30
-90
f1 (ppm)



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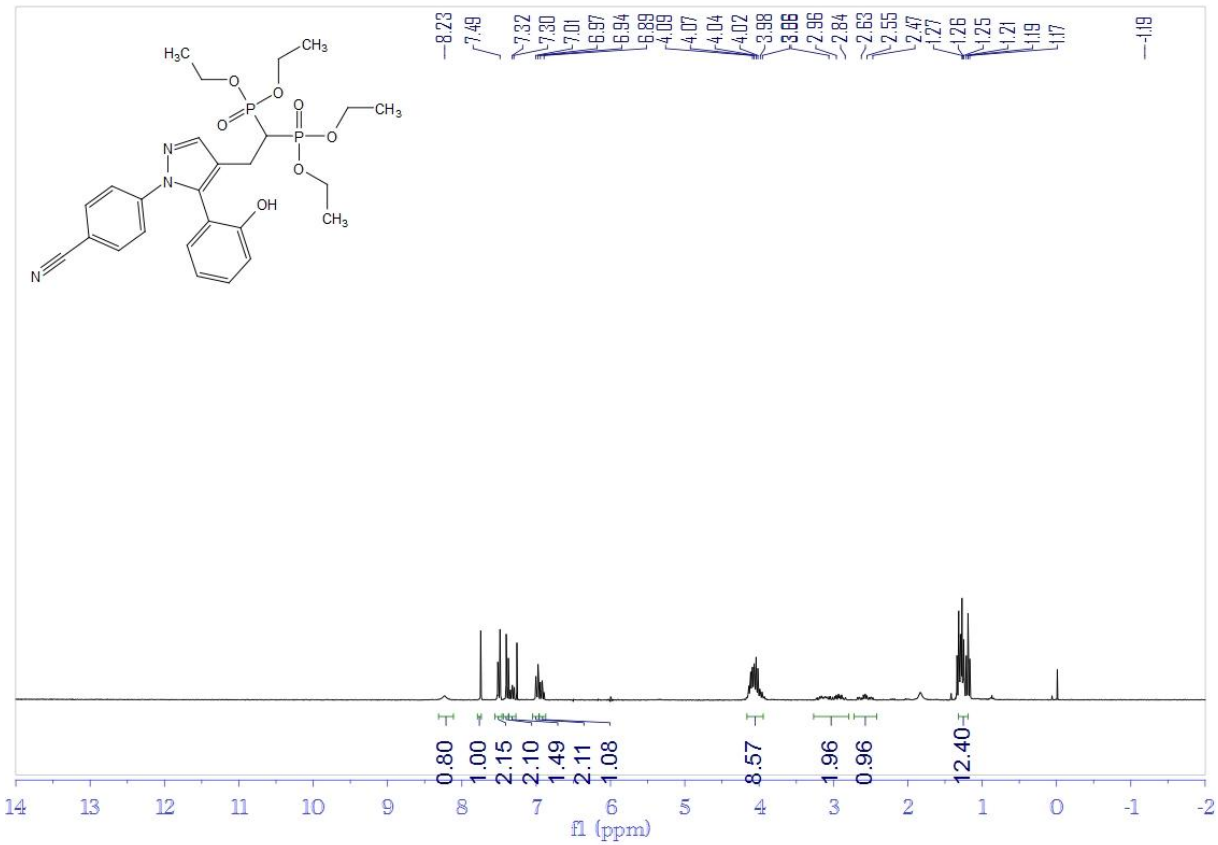
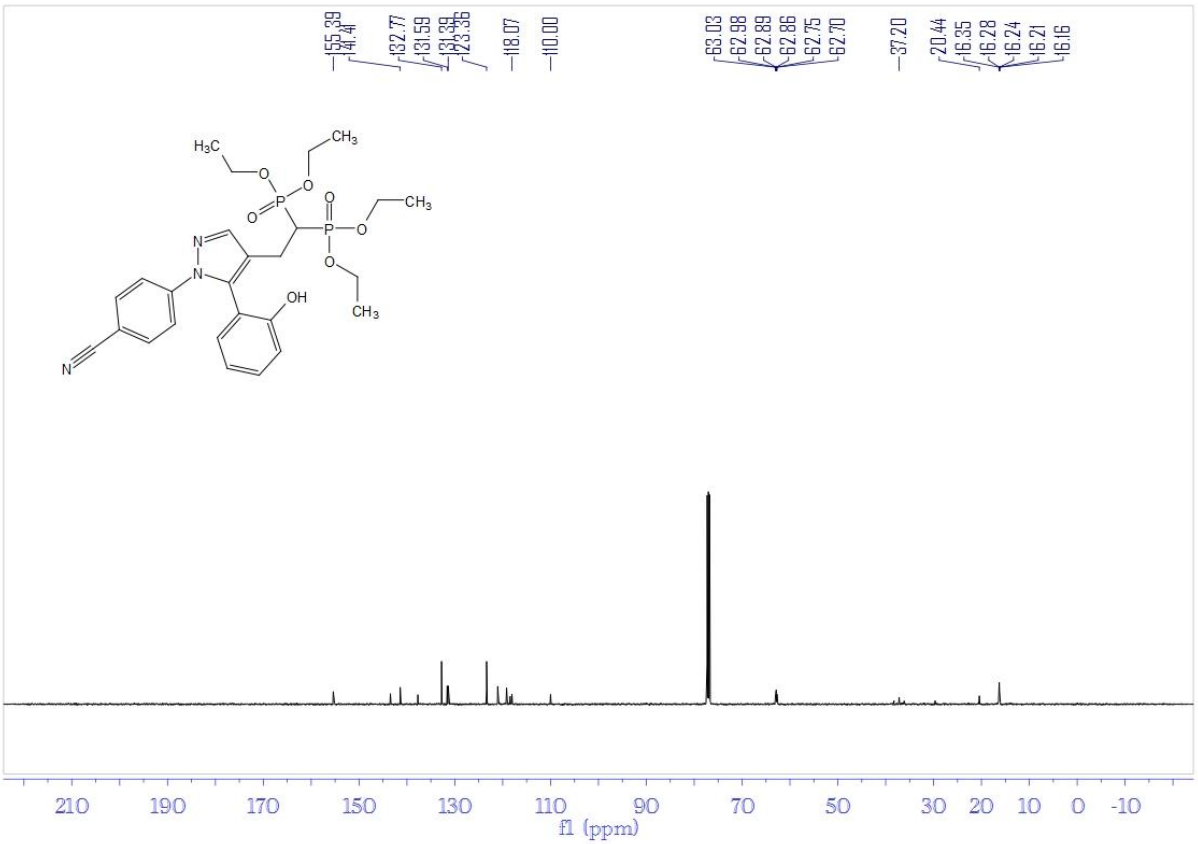
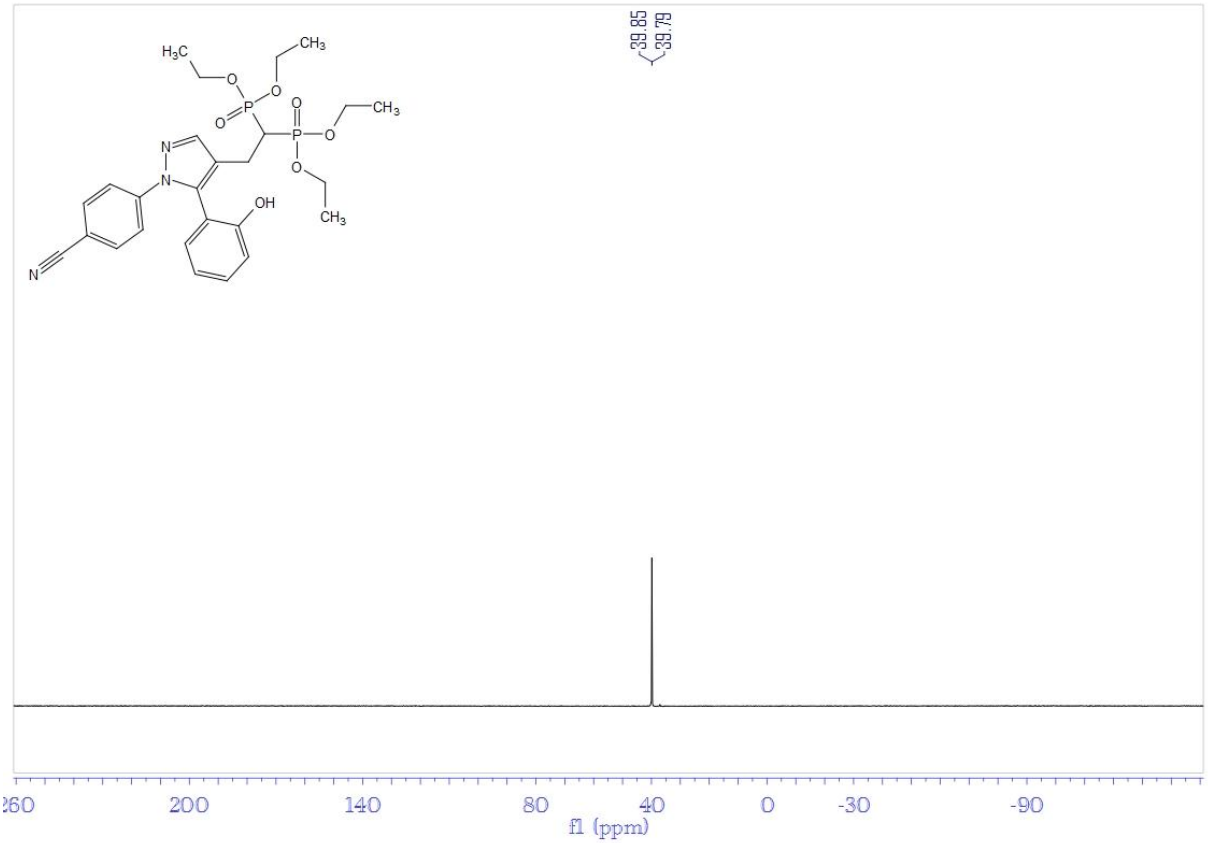
260
200
140
80
40
0
-30
-90
f1 (ppm)


8.23
7.49
7.32
7.30
7.01
6.97
6.94
6.89
4.09
4.07
4.04
4.02
3.98
3.96
3.86
2.96
2.84
2.63
2.55
2.47
1.27
1.26
1.25
1.21
1.19
1.17
1.19
0.80
1.00
2.15
2.10
1.49
2.11
1.08
8.57
1.96
0.96
12.40
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
f1 (ppm)


155.39
147.41
132.77
131.59
123.35
118.07
110.00
63.03
62.98
62.89
62.86
62.75
62.70
37.20
20.44
16.35
16.28
16.24
16.21
16.16
210
190
170
150
130
110
90
70
50
30
20
10
0
-10
f1 (ppm)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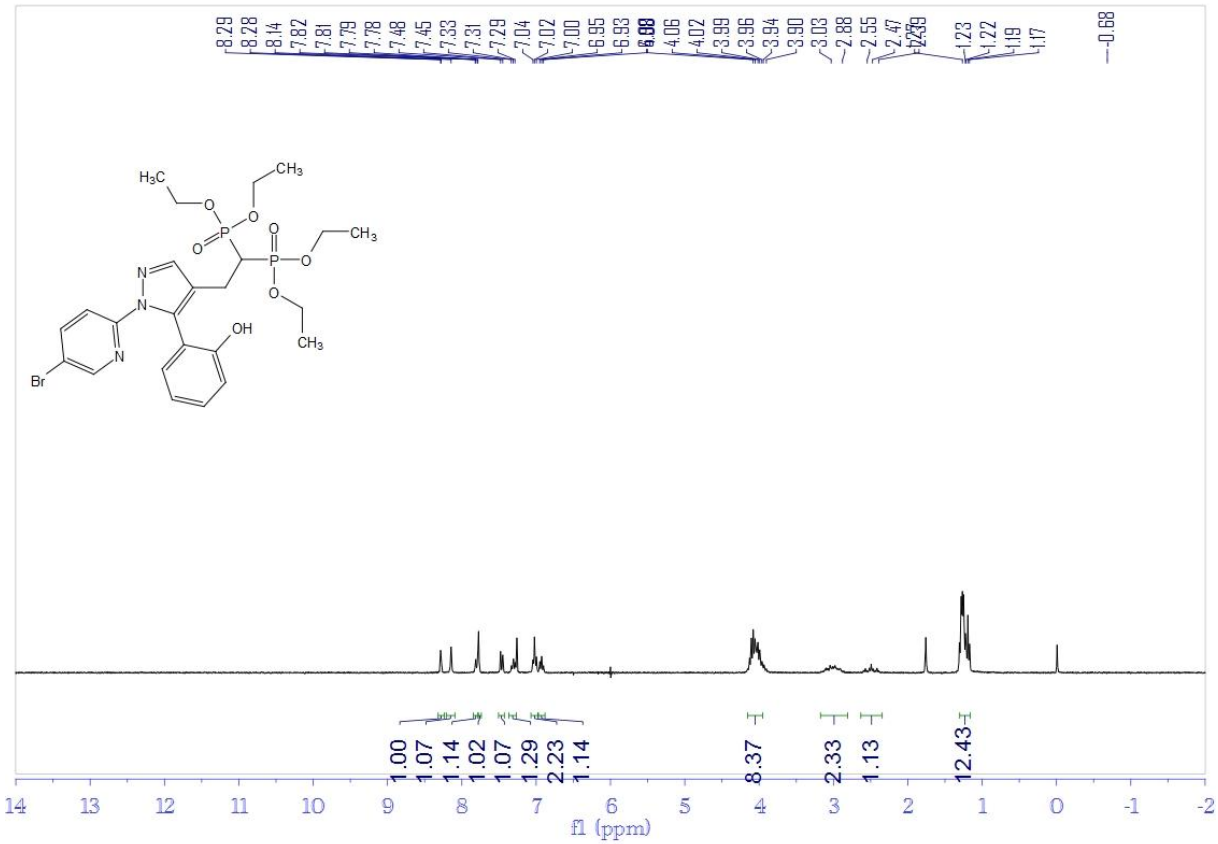
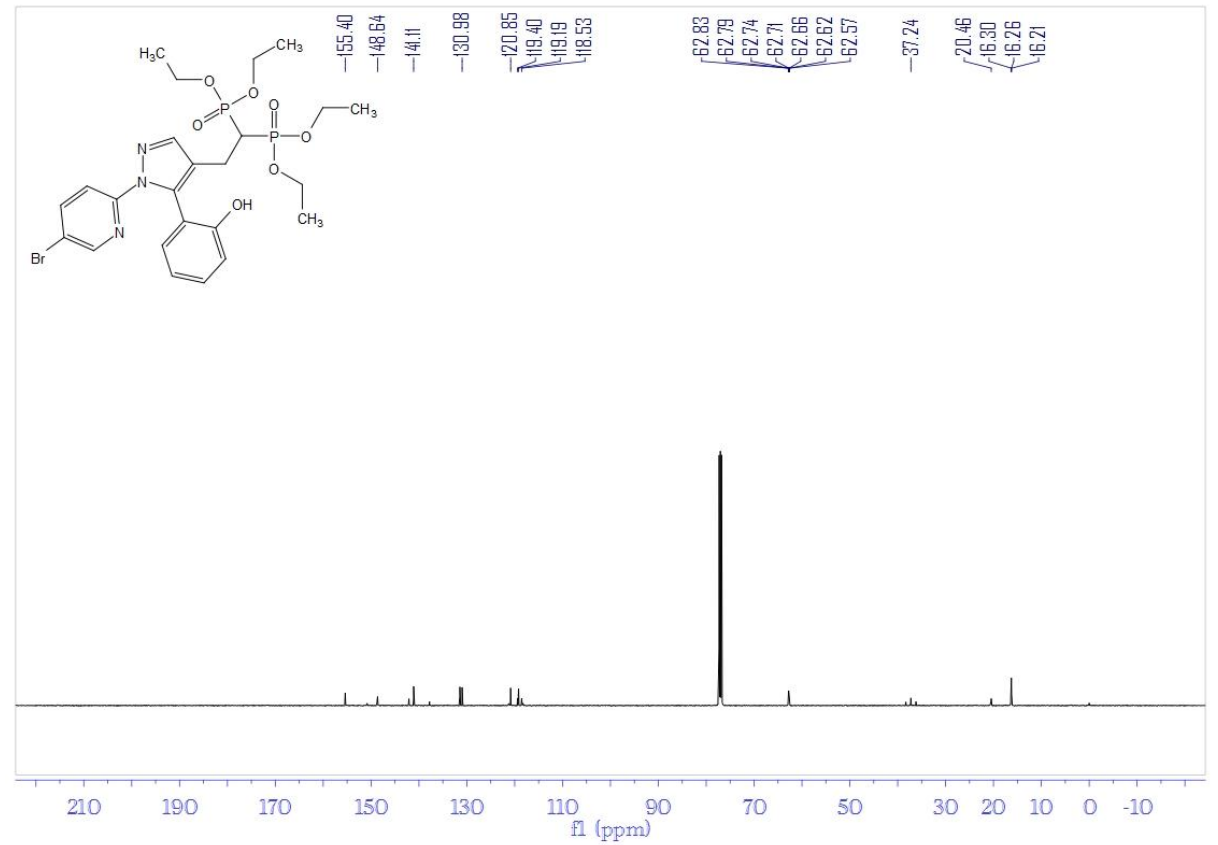
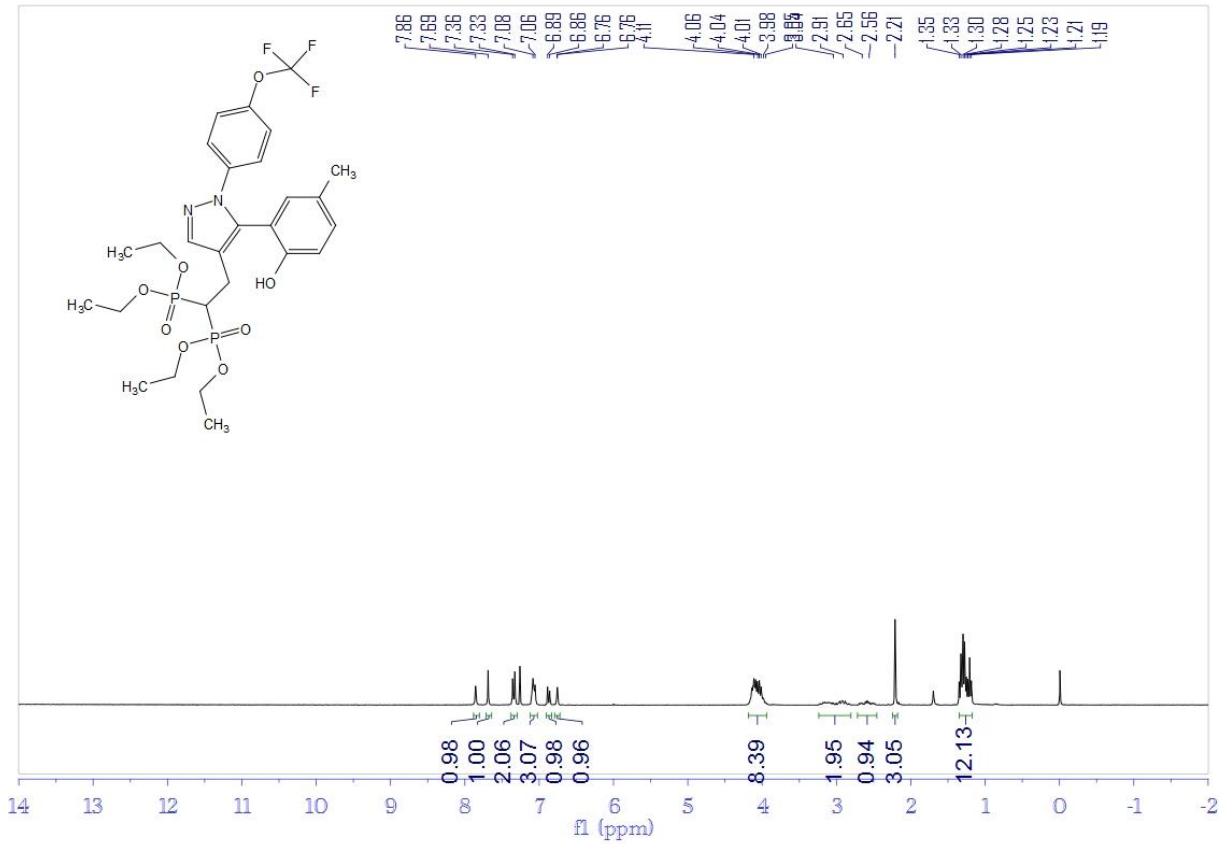
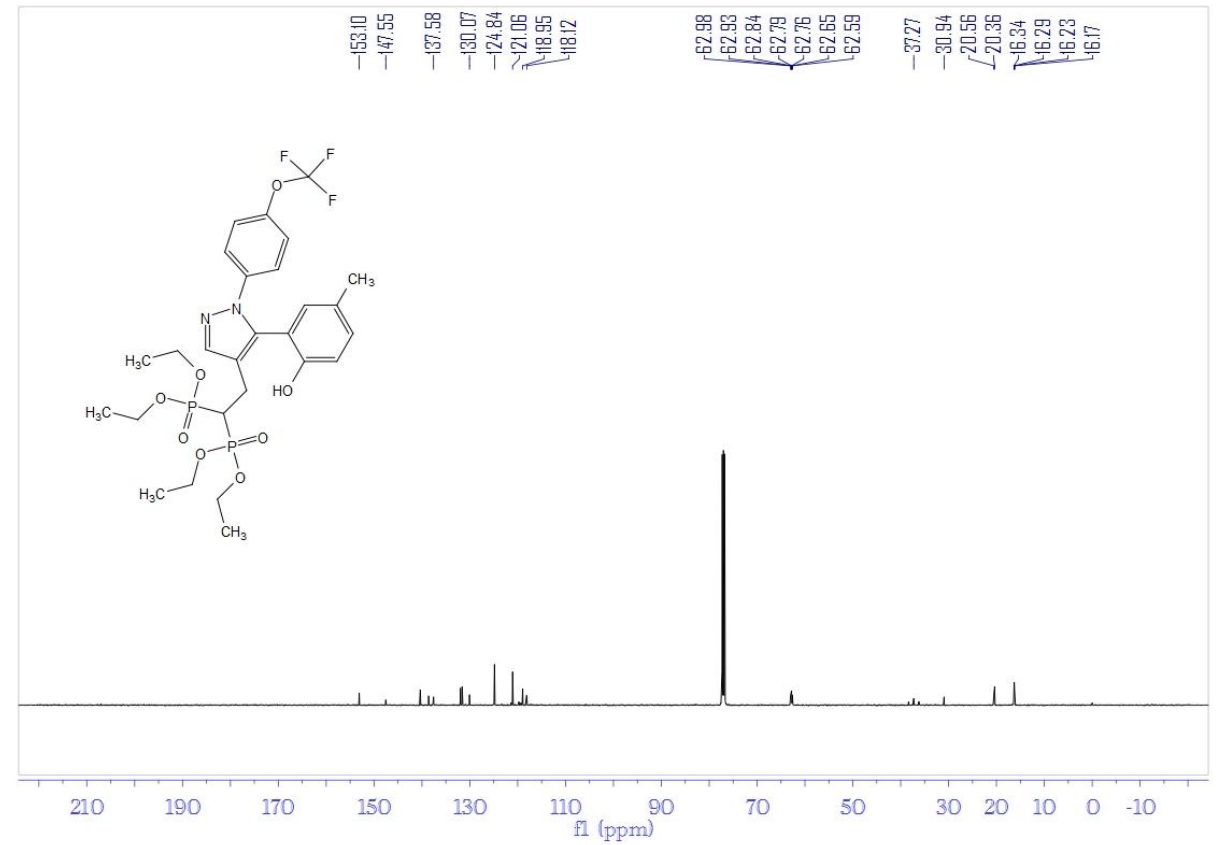
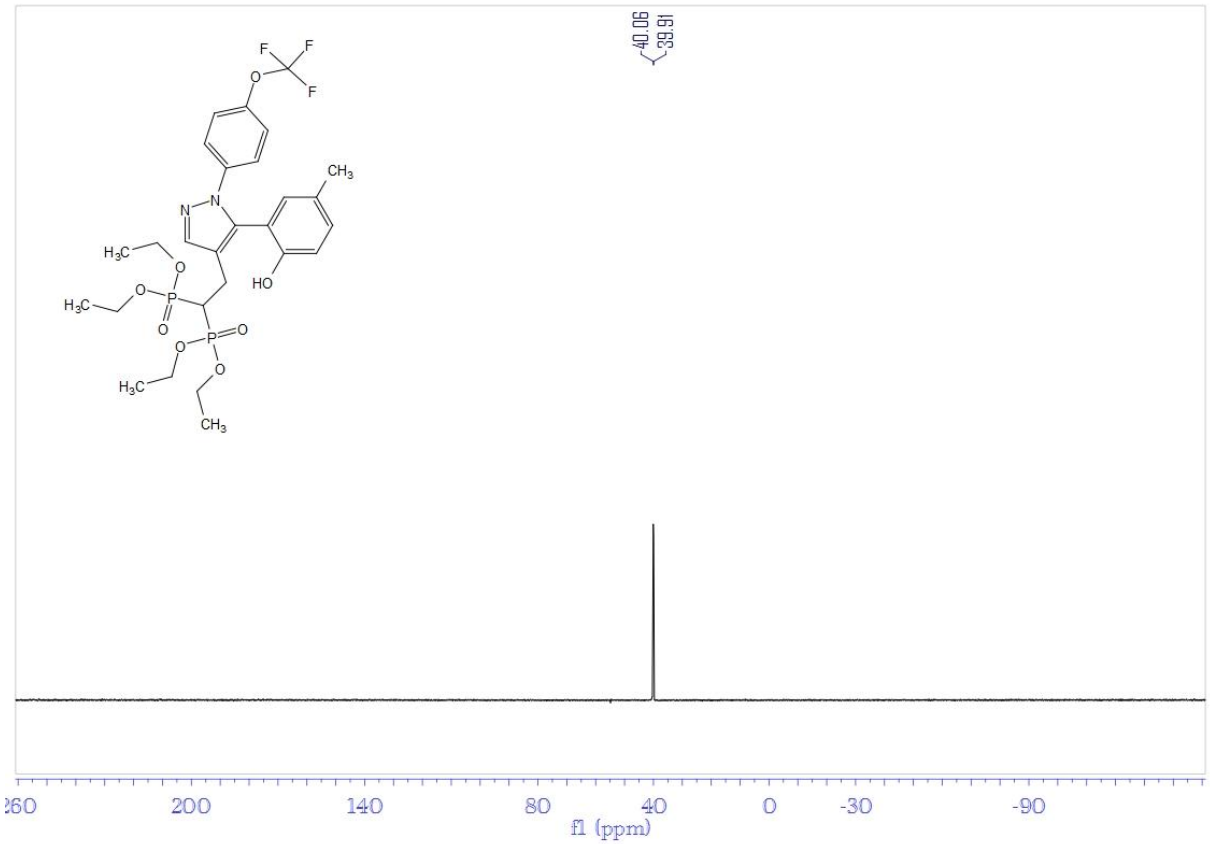
39.79
260
200
140
80
40
0
-30
-90
f1 (ppm)

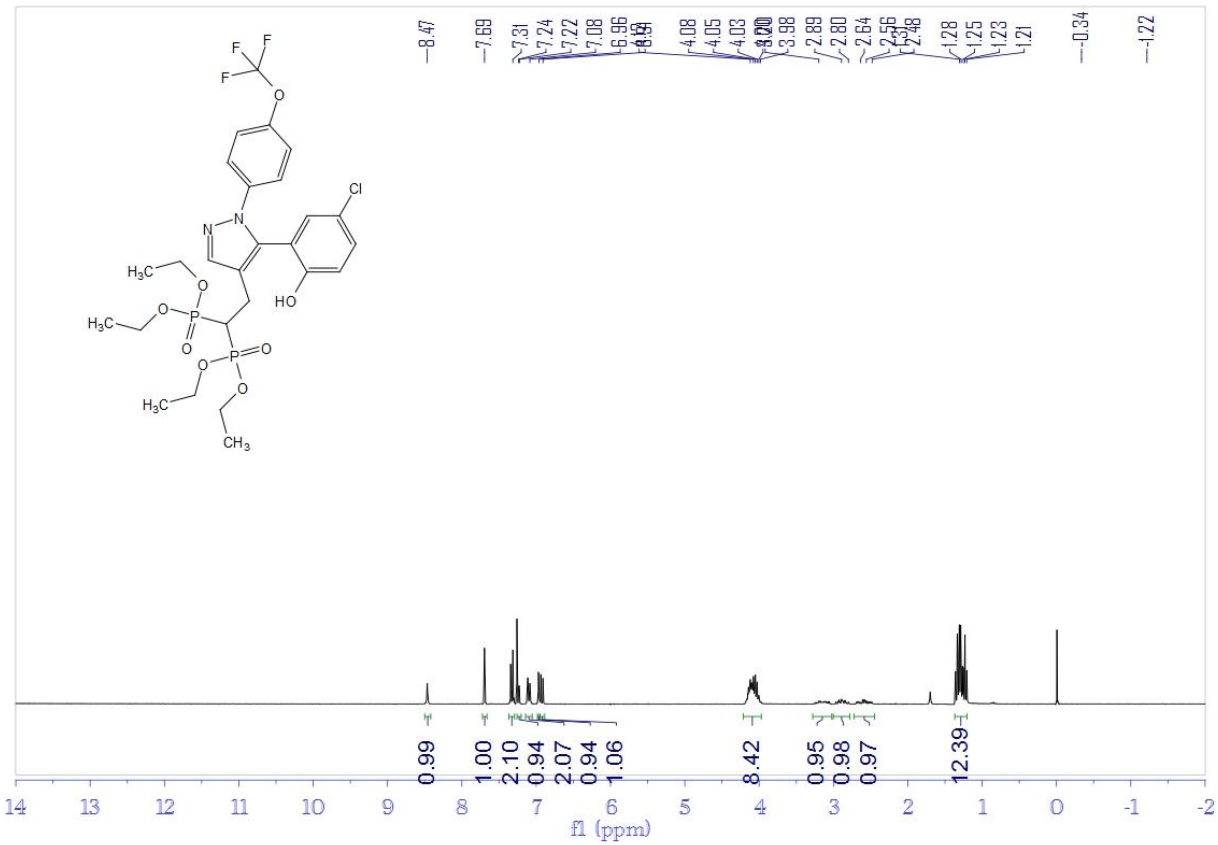

8.29
8.28
8.14
7.82
7.81
7.79
7.78
7.48
7.45
7.33
7.31
7.29
7.04
7.02
7.00
6.95
6.93
4.06
4.02
3.99
3.96
3.94
3.90
3.03
2.88
2.55
2.47
1.23
1.22
1.19
1.17
-0.68
1.00
1.07
1.14
1.02
1.07
1.29
2.23
1.14
8.37
2.33
1.13
12.43
f1 (ppm)

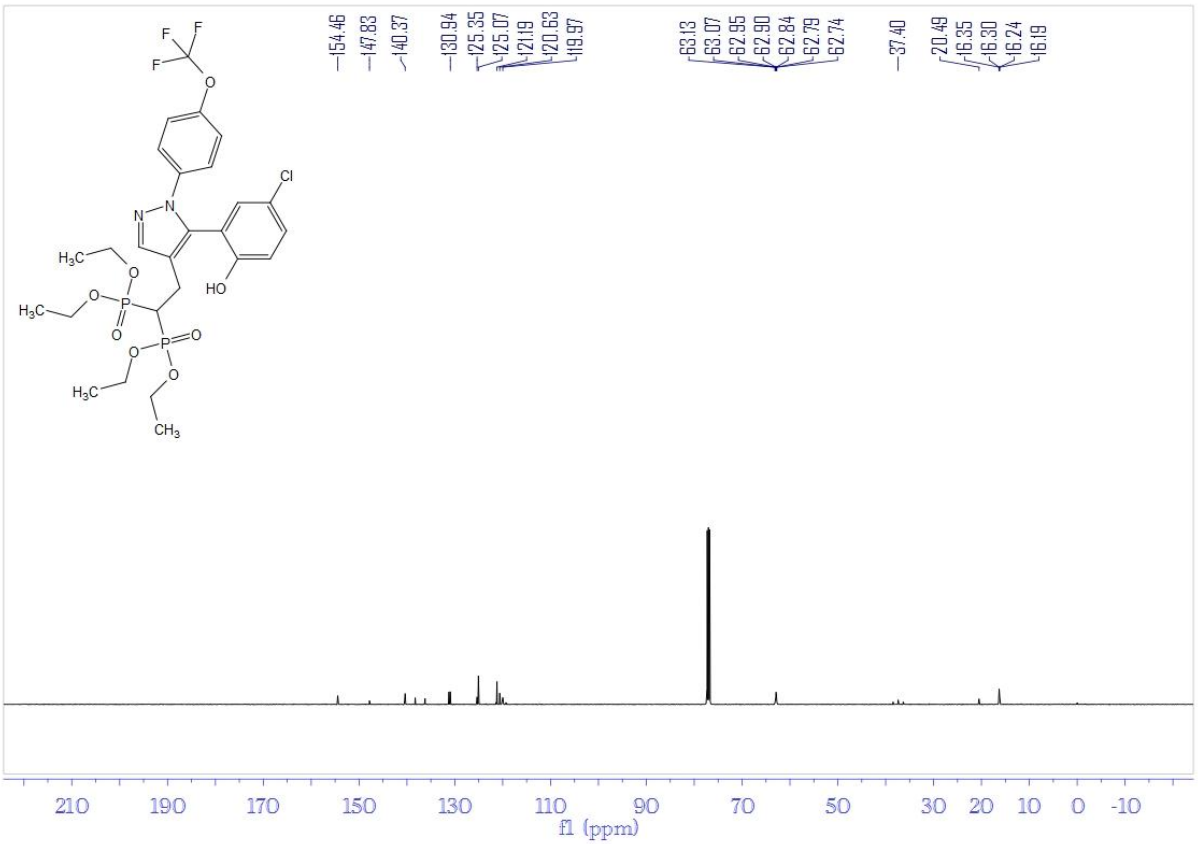

155.40
148.64
141.11
130.98
120.85
119.40
119.19
118.53
62.83
62.79
62.74
62.71
62.66
62.62
62.57
37.24
20.46
16.30
16.26
16.21
f1 (ppm)

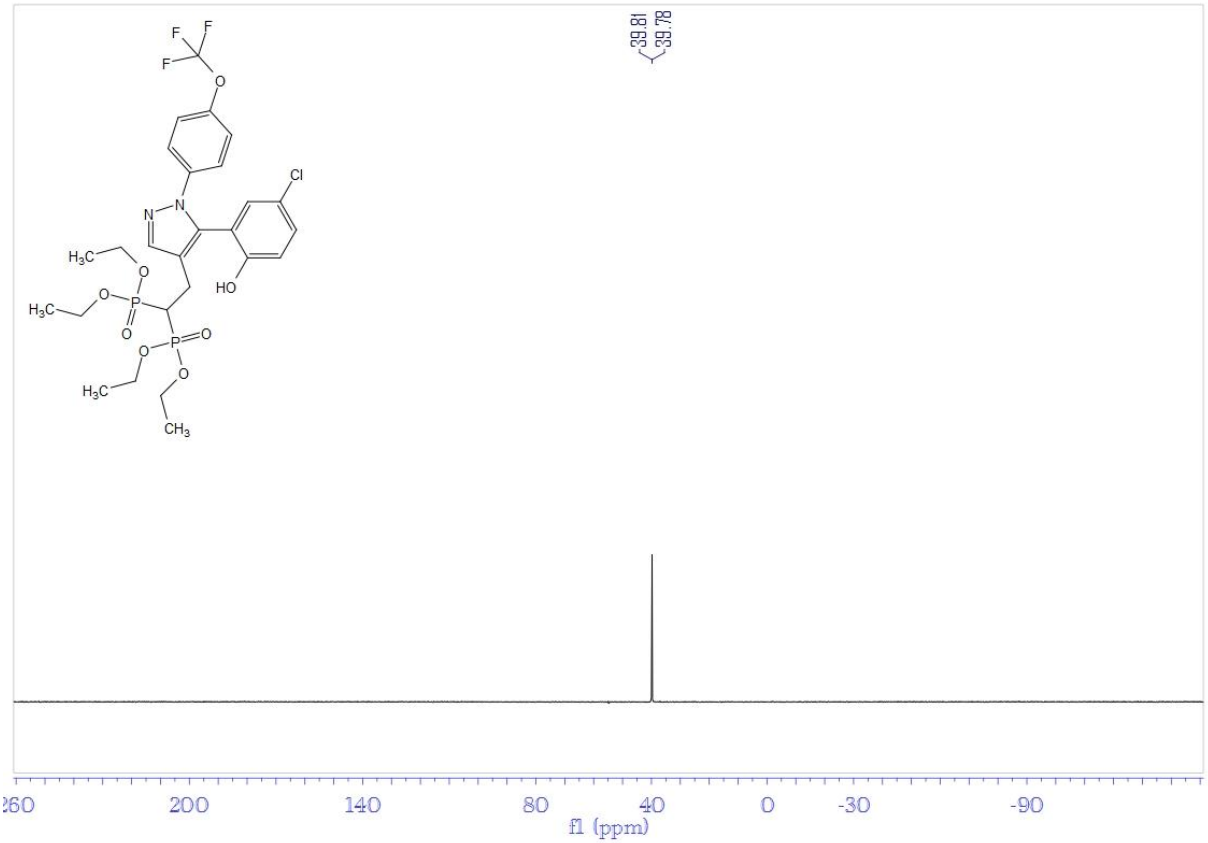


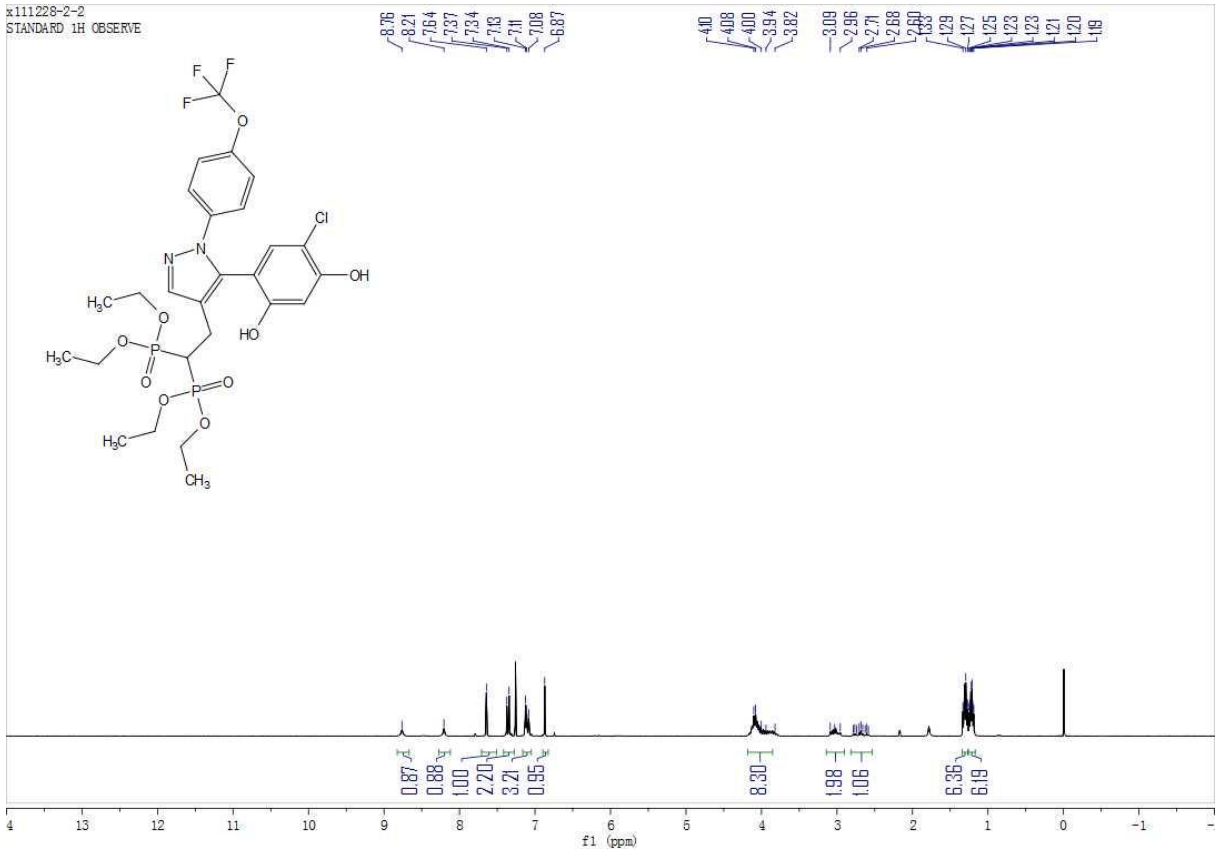


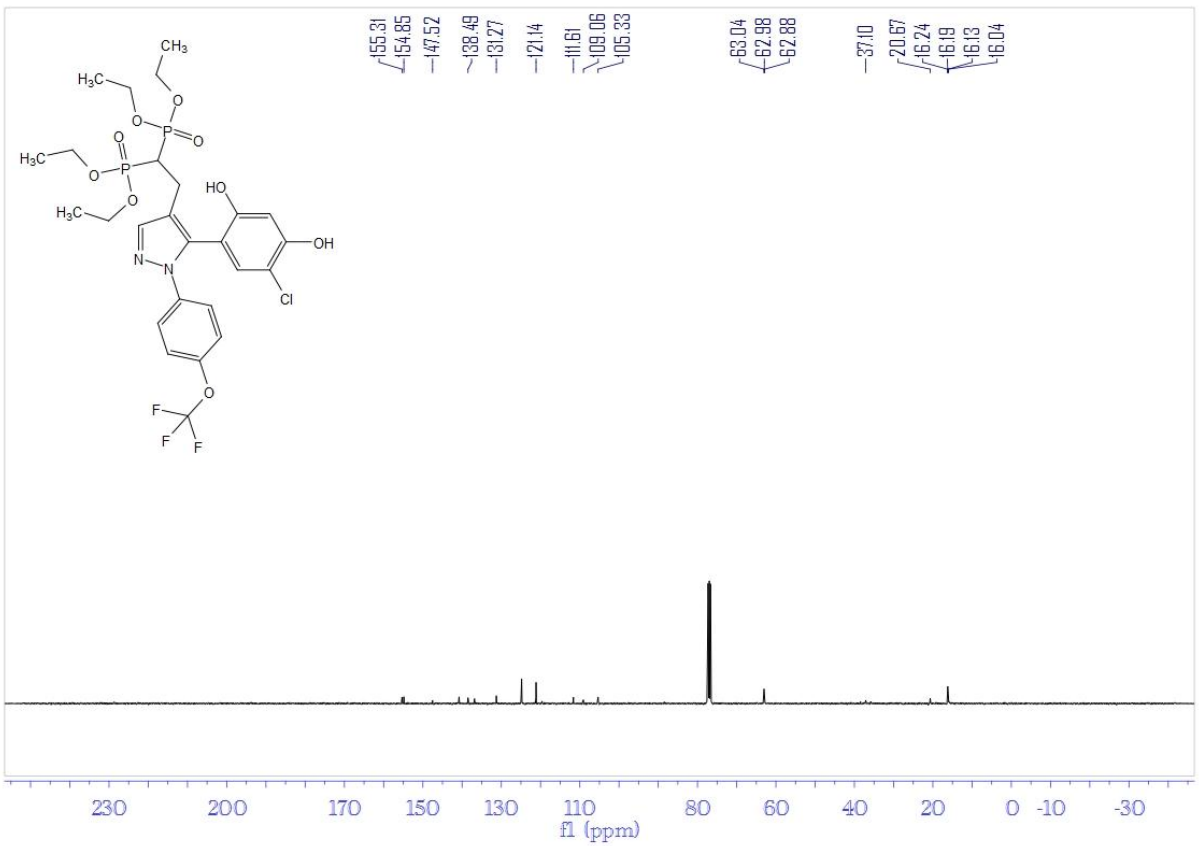

40.06
39.91
f1 (ppm)

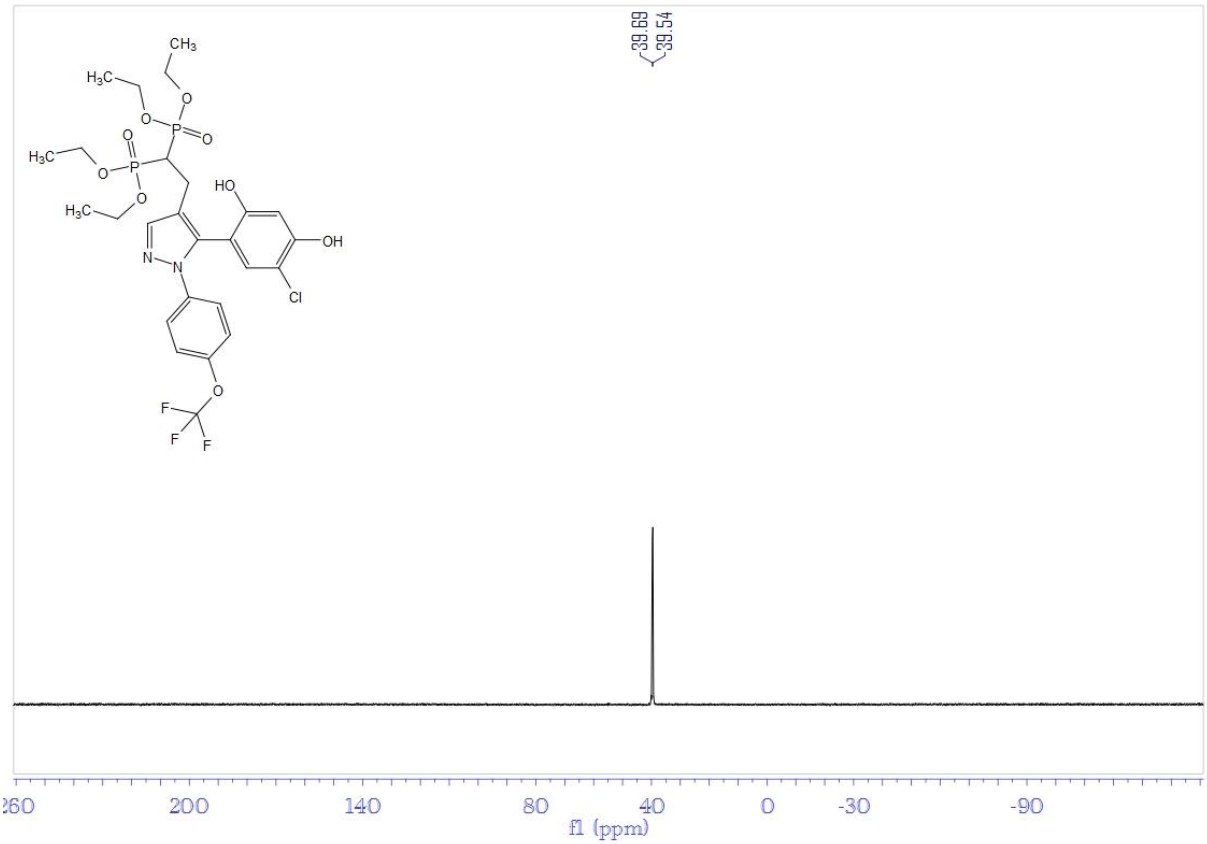

8.47
7.69
7.31
7.24
7.22
7.08
6.96
4.08
4.05
4.03
3.98
2.89
2.80
2.64
2.56
2.48
1.28
1.25
1.23
1.21
0.34
1.22
0.99
1.00
2.10
0.94
2.07
0.94
1.06
8.42
0.95
0.98
0.97
12.39
f1 (ppm)

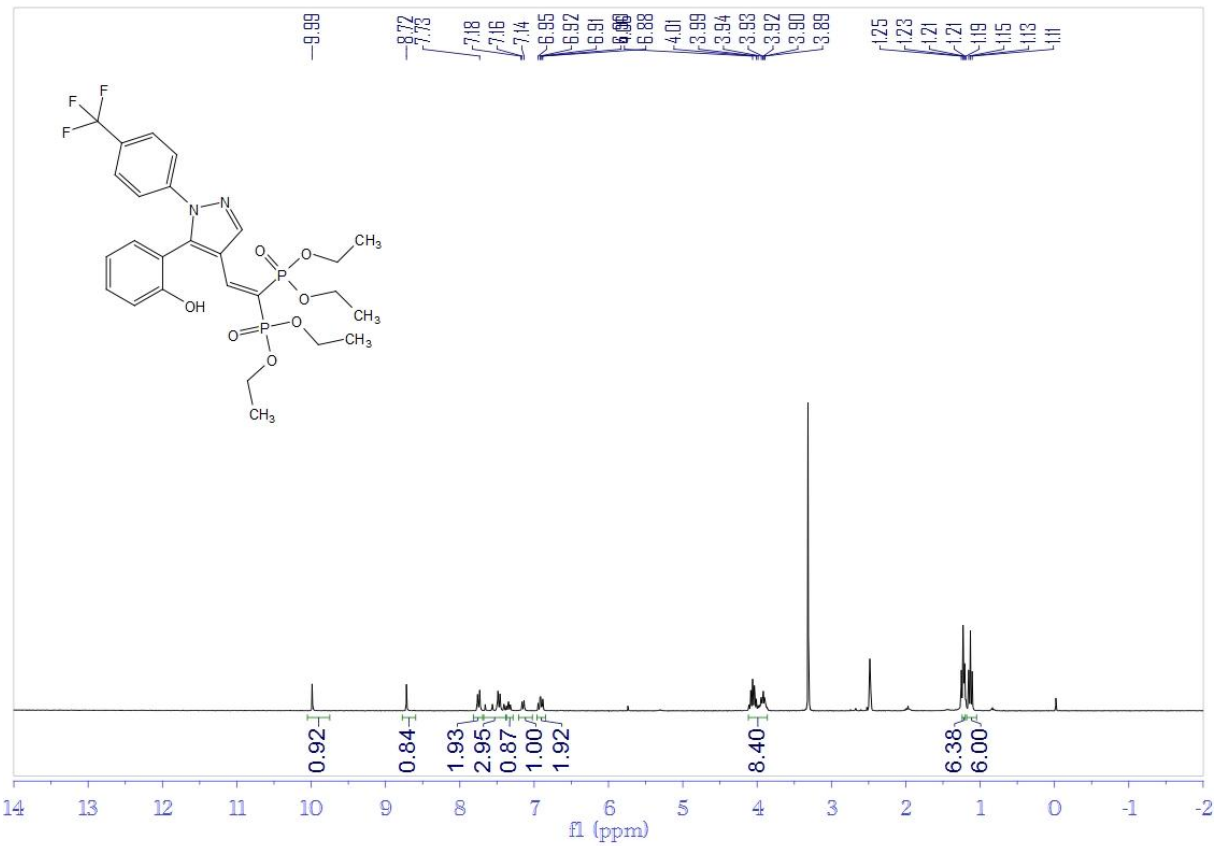

154.46
147.83
140.37
130.94
125.35
125.07
121.19
120.63
119.97
63.13
63.07
62.95
62.90
62.84
62.79
62.74
37.40
20.49
16.35
16.30
16.24
16.19
F
F
F
O
Cl
N
N
H3C
O
HO
O
P
O
H3C
O
O
P
O
O
H3C
O
CH3
210
190
170
150
130
110
90
70
50
30
20
10
0
-10
f1 (ppm)


39.81
39.78
F
F
F
O
Cl
N
N
H3C
O
HO
O
P
O
H3C
O
O
P
O
O
H3C
O
CH3
260
200
140
80
40
0
-30
-90
f1 (ppm)


x111228-2-2
STANDARD 1H OBSERVE
f1 (ppm)


f1 (ppm)


39.69
39.54
260
200
140
80
40
0
-30
-90
f1 (ppm)


9.99
8.72
7.73
7.18
7.16
7.14
6.95
6.92
6.91
6.88
4.01
3.99
3.94
3.93
3.92
3.90
3.89
1.25
1.23
1.21
1.21
1.19
1.15
1.13
1.11
0.92
0.84
1.93
2.95
0.87
1.00
1.92
8.40
6.38
6.00
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
f1 (ppm)