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Coláiste na hOllscoile Corcaigh

Supplementary data

Synthesis, evaluation and mechanistic insights of novel IMPDH inhibitors targeting ESKAPEE bacteria

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**These authors contributed equally*

‡These authors contributed also equally

#Corresponding authors

Affiliation

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[g]Sorbonne Université, INSERM, CNRS, Neuroscience Paris Seine - Institut de Biologie Paris Seine (NPS - IBPS), F-75005 Paris, France

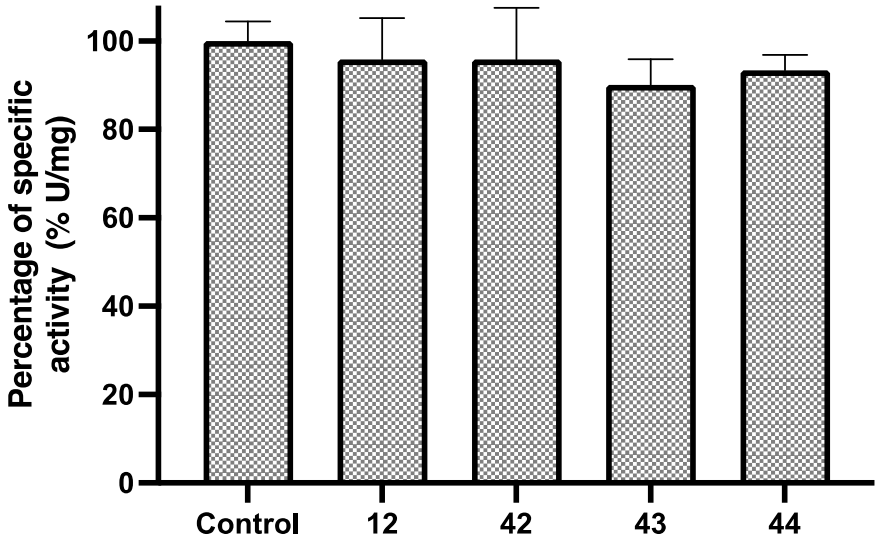


Figure S1. Assays on human IMPDH. Histogram representation of the % of the hIMPDH2 specific activity in the absence (control) or in the presence of 50 μM of **12**, **42**, **43** or **44**.

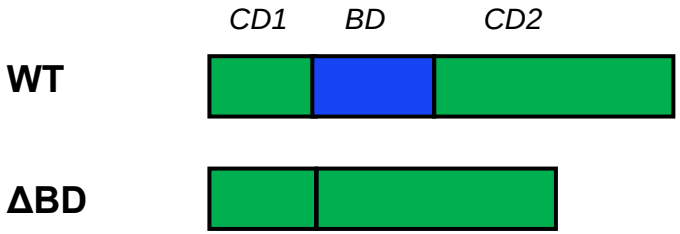


Figure S2. Schematic organization of the WT IMPDH and its ΔDB variant.

The IMPDH monomer is organized into two structural domains, the core domain (CD) in green containing the catalytic site and the Bateman domain (BD) in blue. In the primary structure, this later divides the former into two parts noted CD1 and CD2. The ΔDB variant consists of an IMPDH deleted of its Bateman domain, where the two parts CD1 and CD2 are directly linked together.

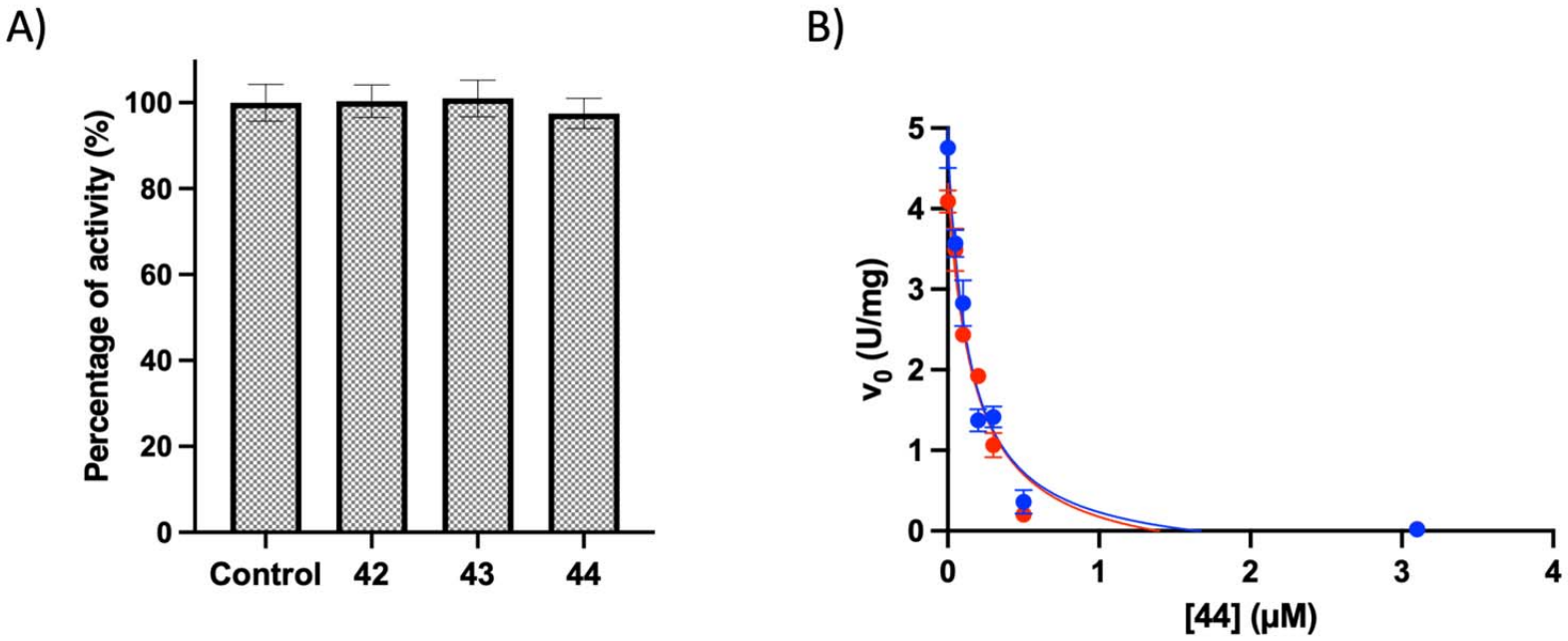
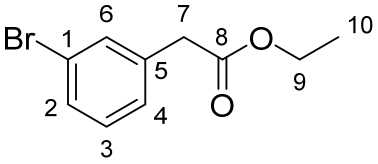
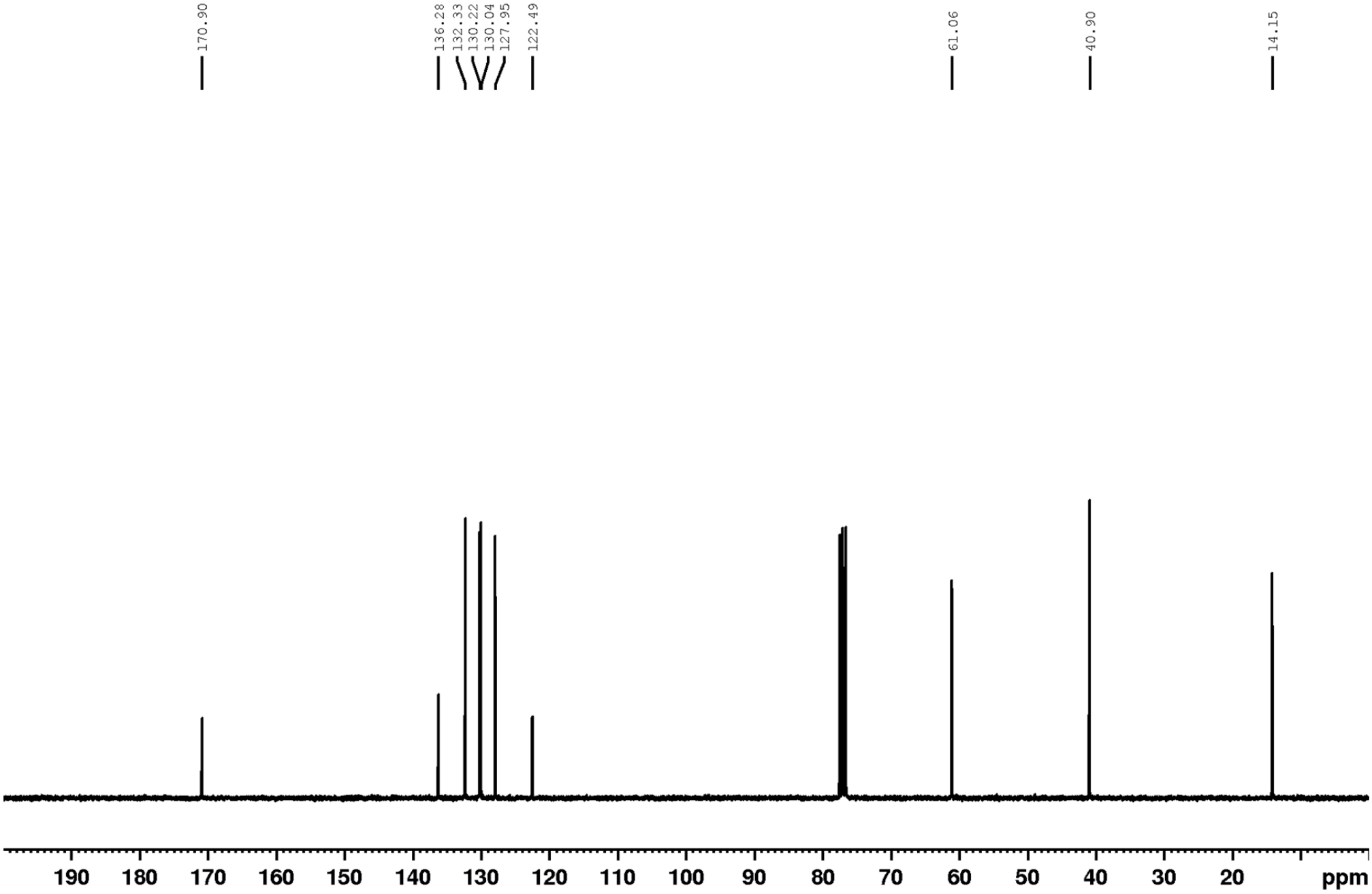


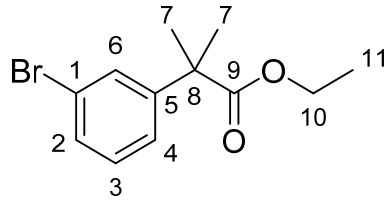
Figure S3. Ruling out promiscuous inhibition by compounds **42**-**44**. A) Histogram representation of the % of catalytic activity of TMP kinase from *M. tuberculosis* in the presence of 20 μM of each compound. The control was performed in the presence of DMSO. B) Dose-response plot of the activity of IMPDHpa ΔBD at variable concentrations of **44** in the presence (blue) or in the absence (red) of 0.01 % Triton X-100.

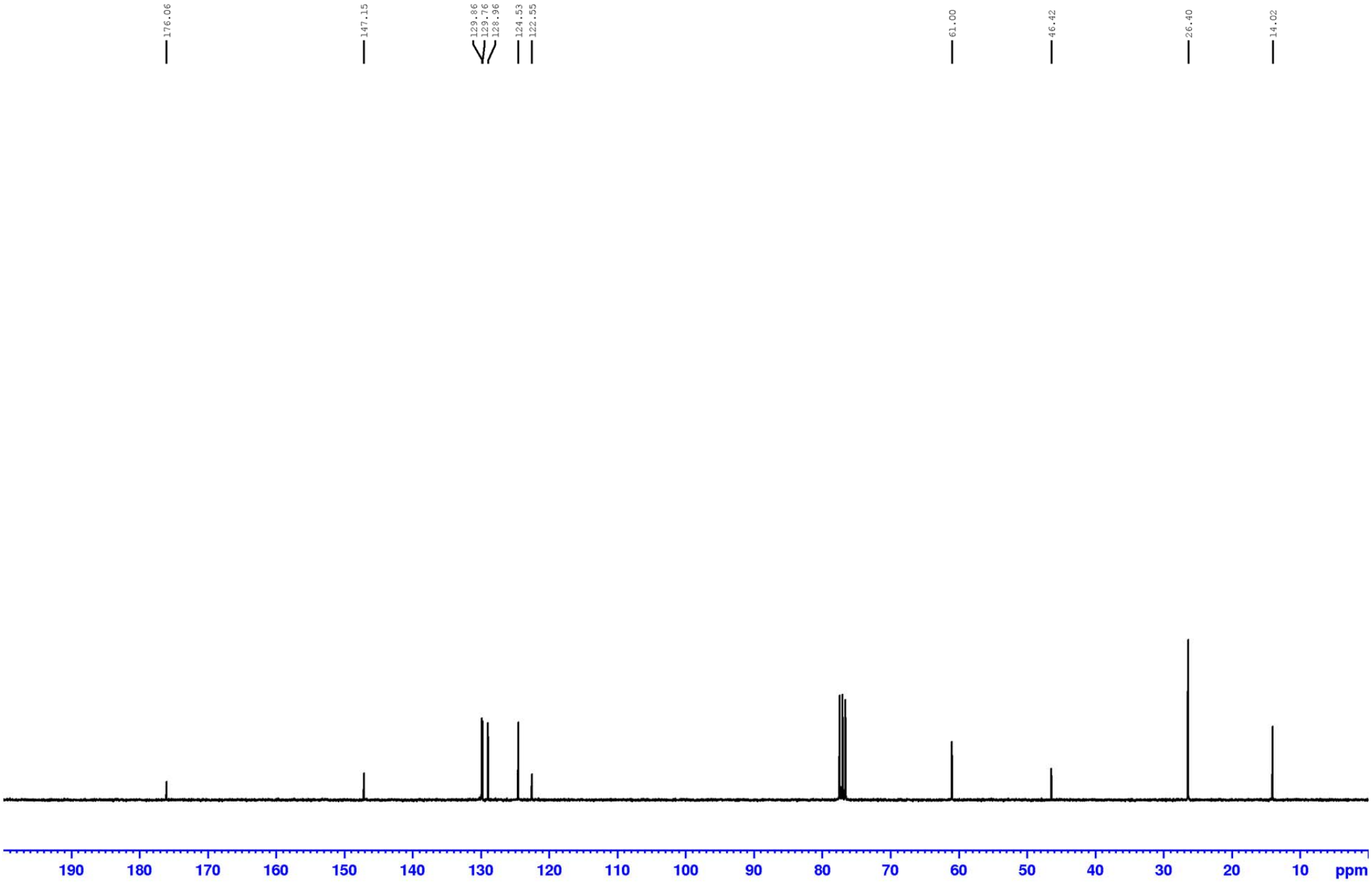
ethyl-2-(3-bromophenyl)acetate (6)



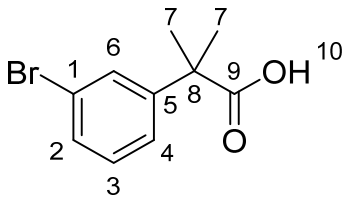

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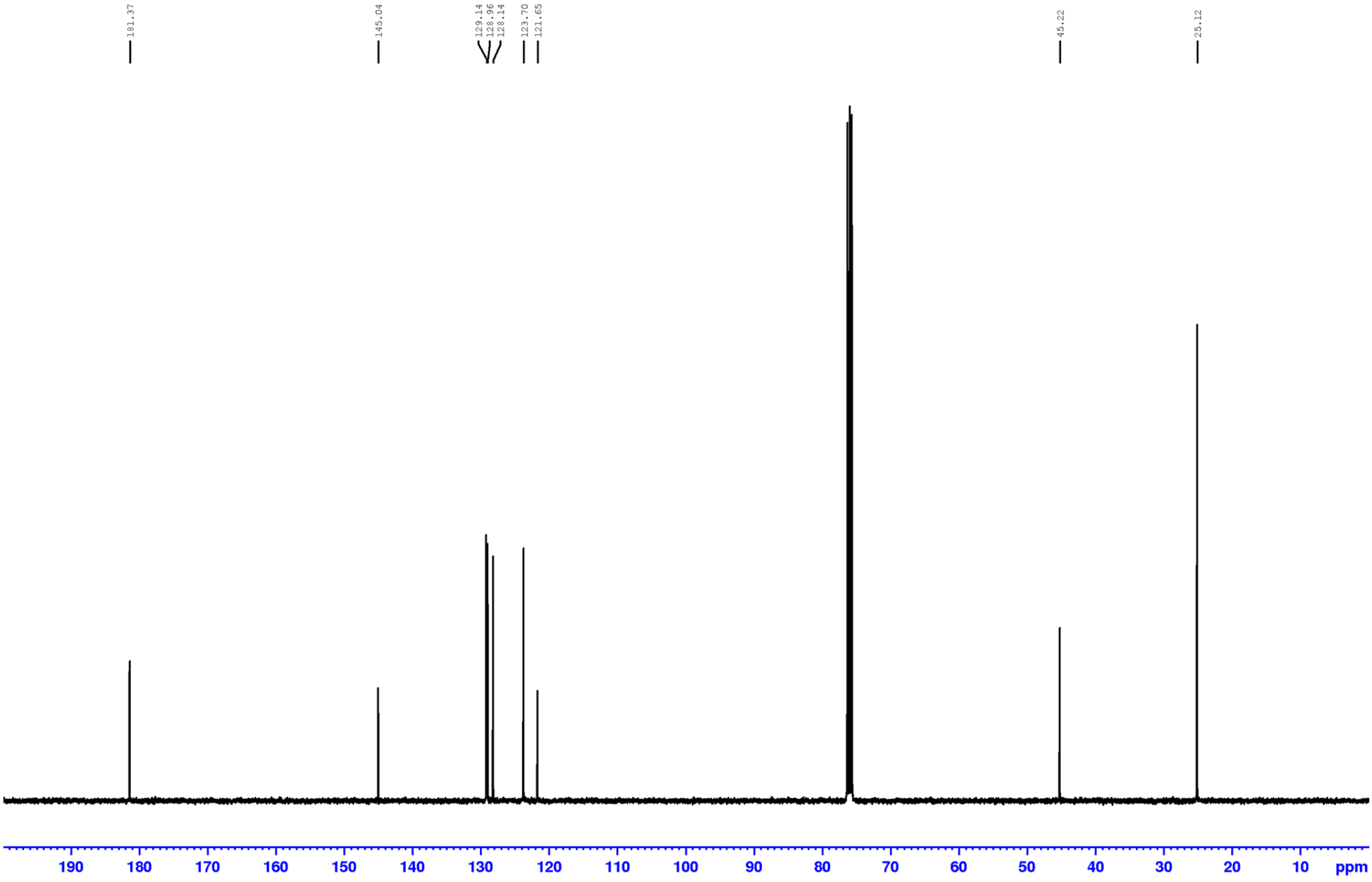
ethyl-2-(3-bromophenyl)-2-methylpropanoate (**7**)



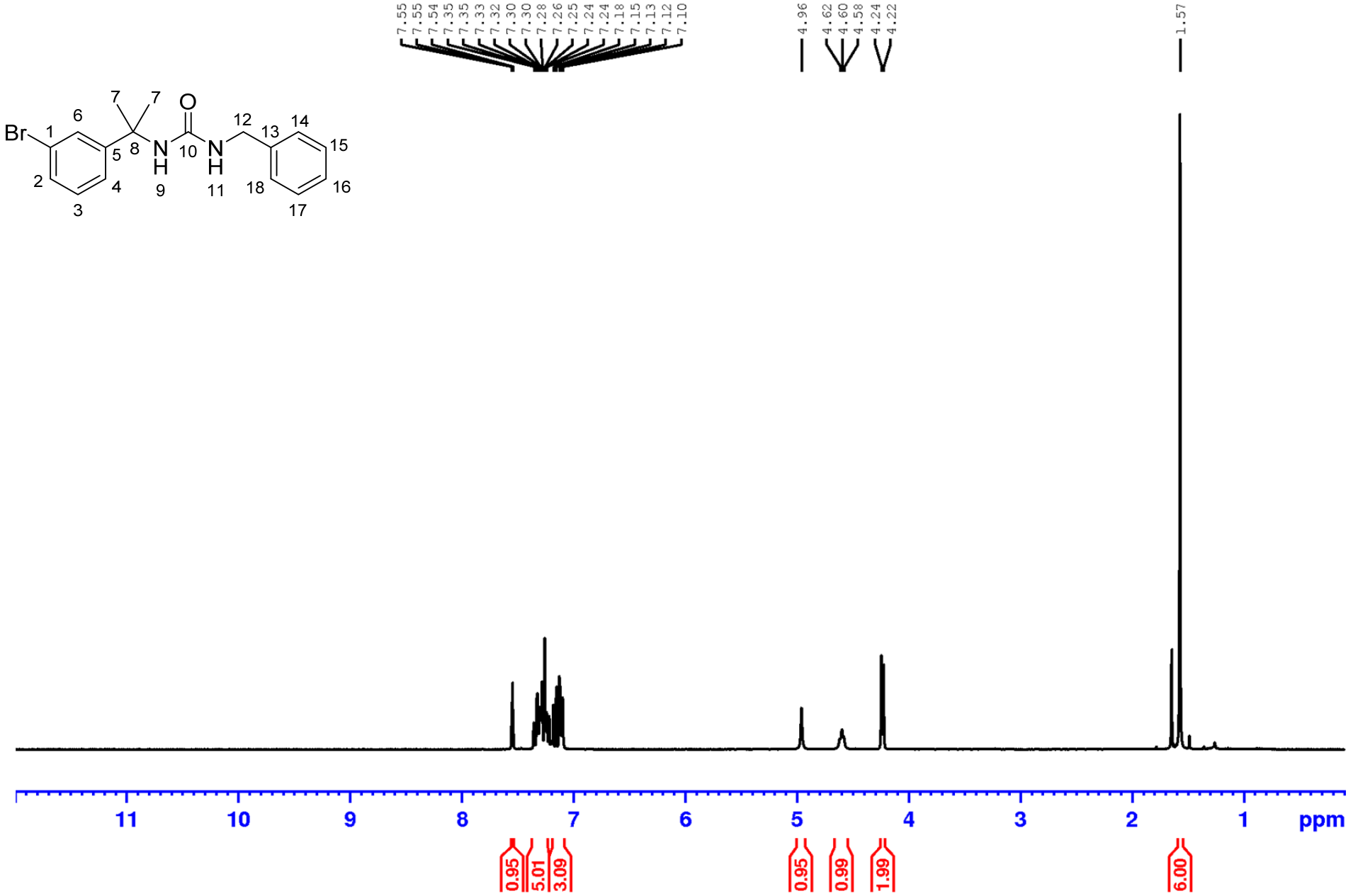

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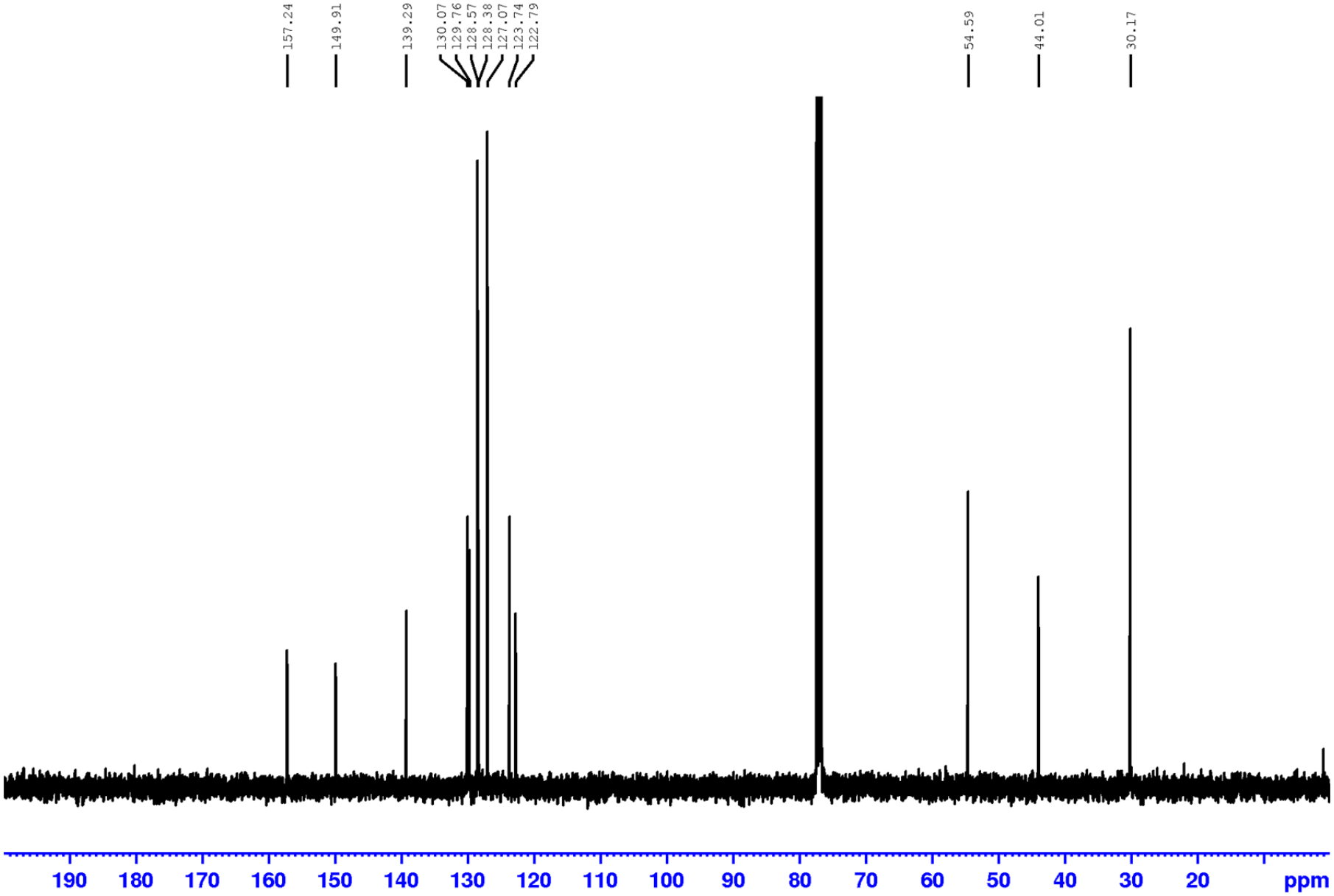
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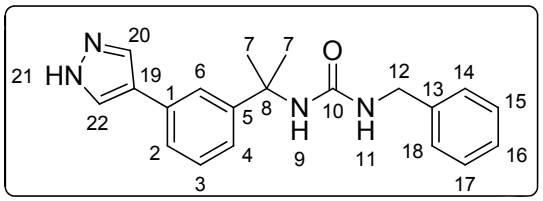

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1-benzyl-3-(2-(3-bromophenyl)propan-2-yl)urea (9)

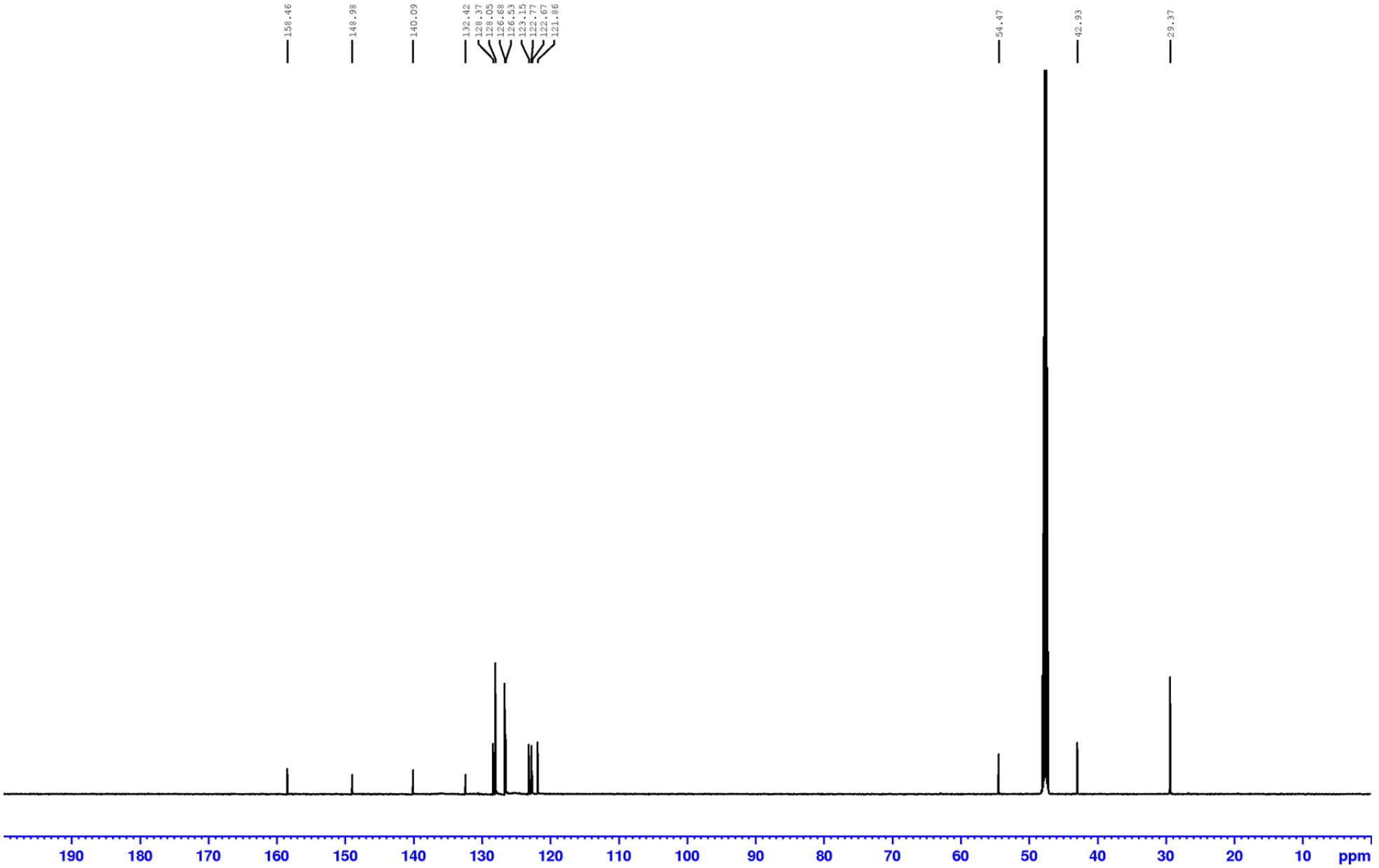



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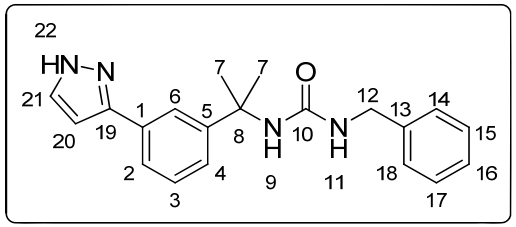
1-(2-(3-(1*H*-pyrazol-4-yl)phenyl)propan-2-yl)-3-benzylurea (10)

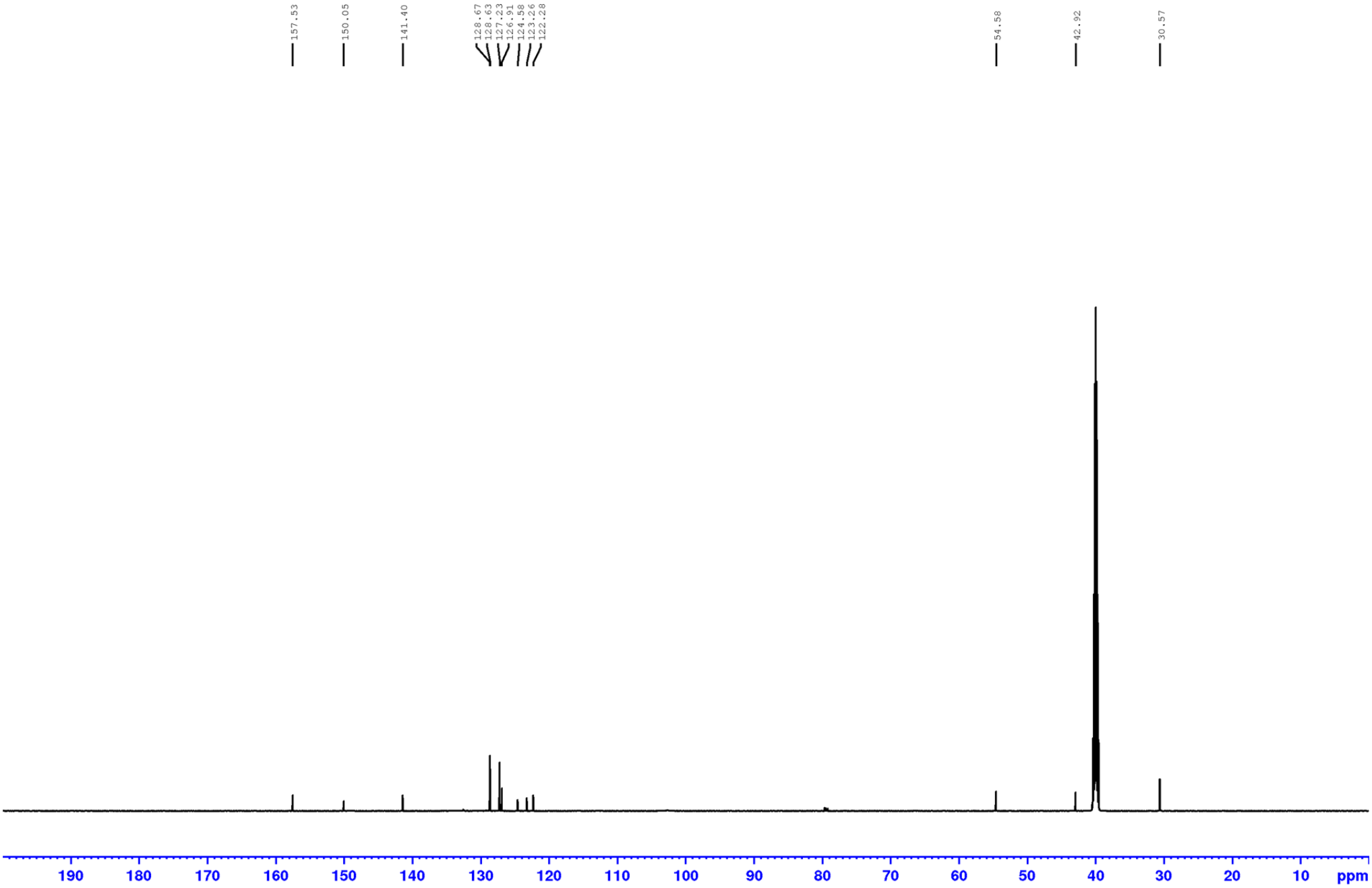


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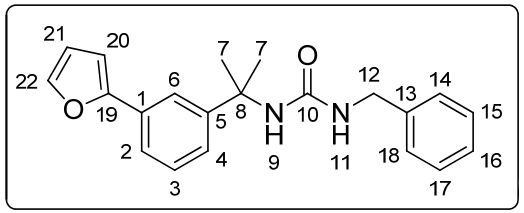

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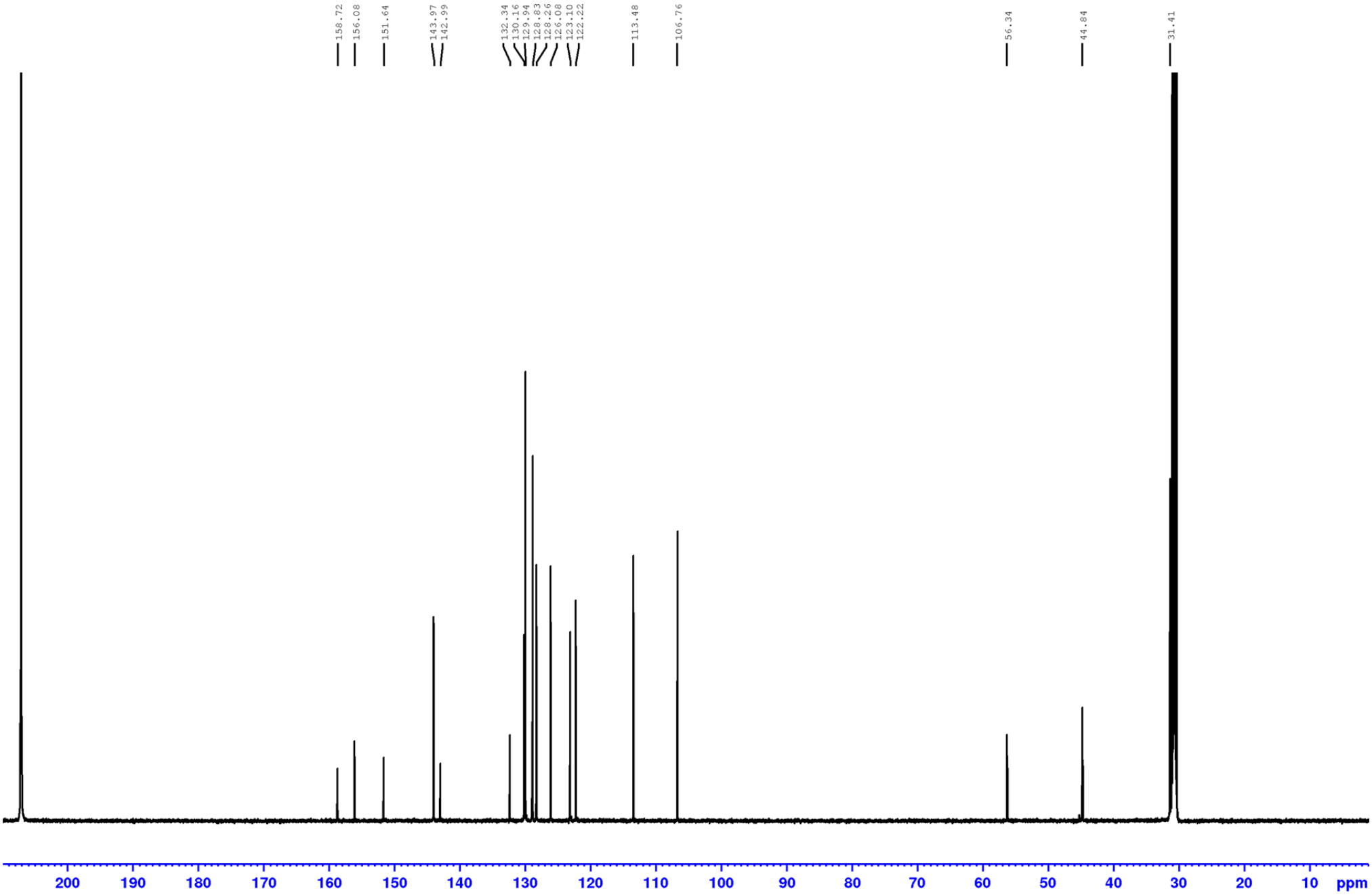
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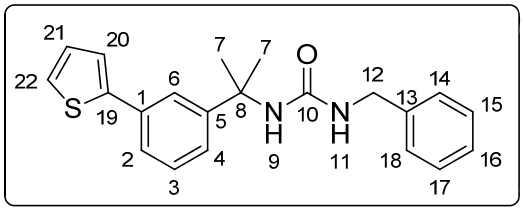

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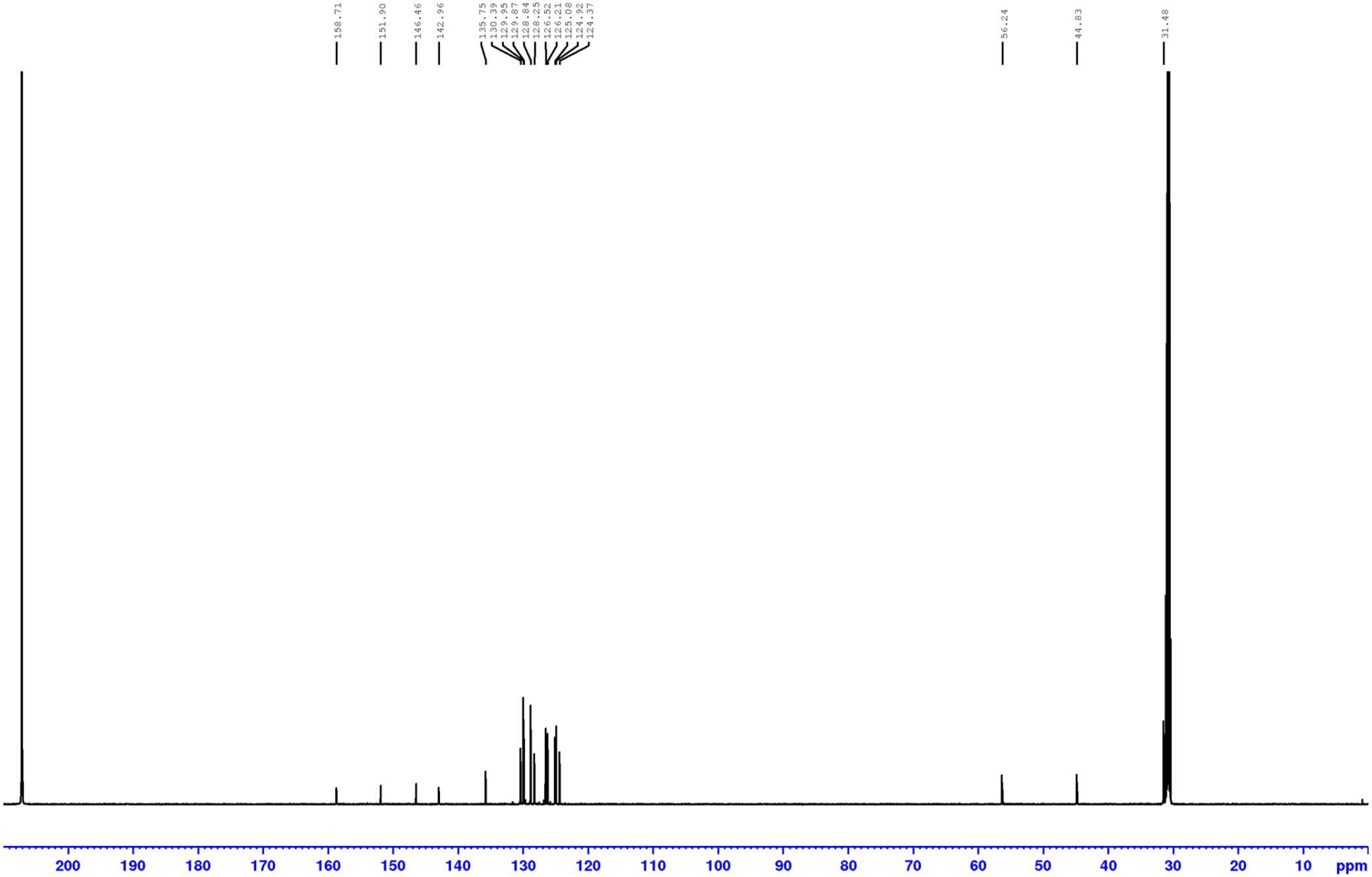
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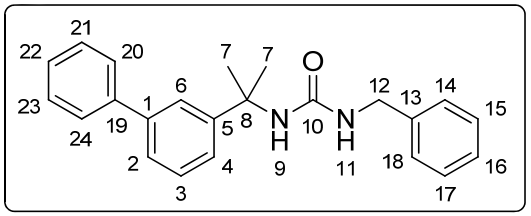

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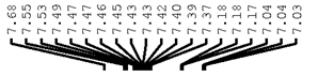
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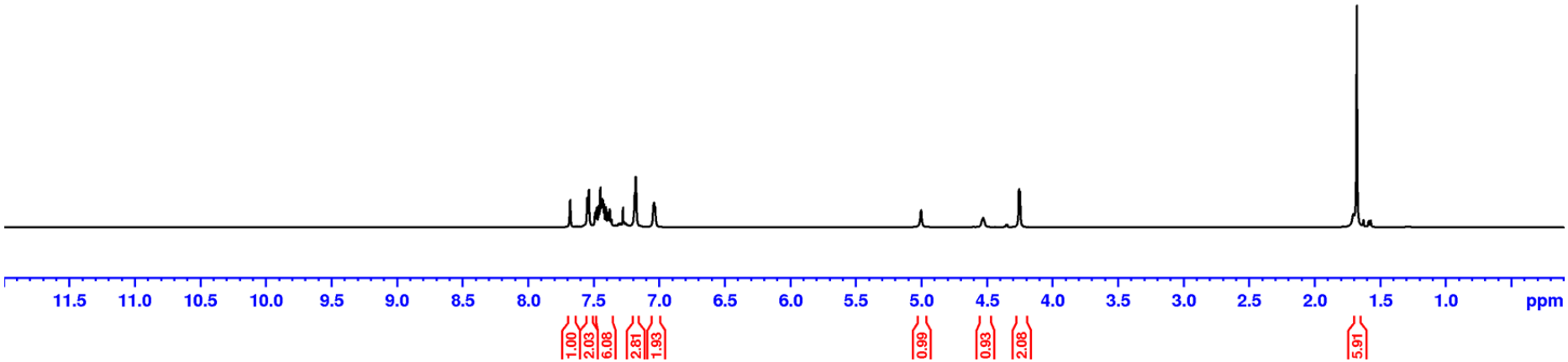

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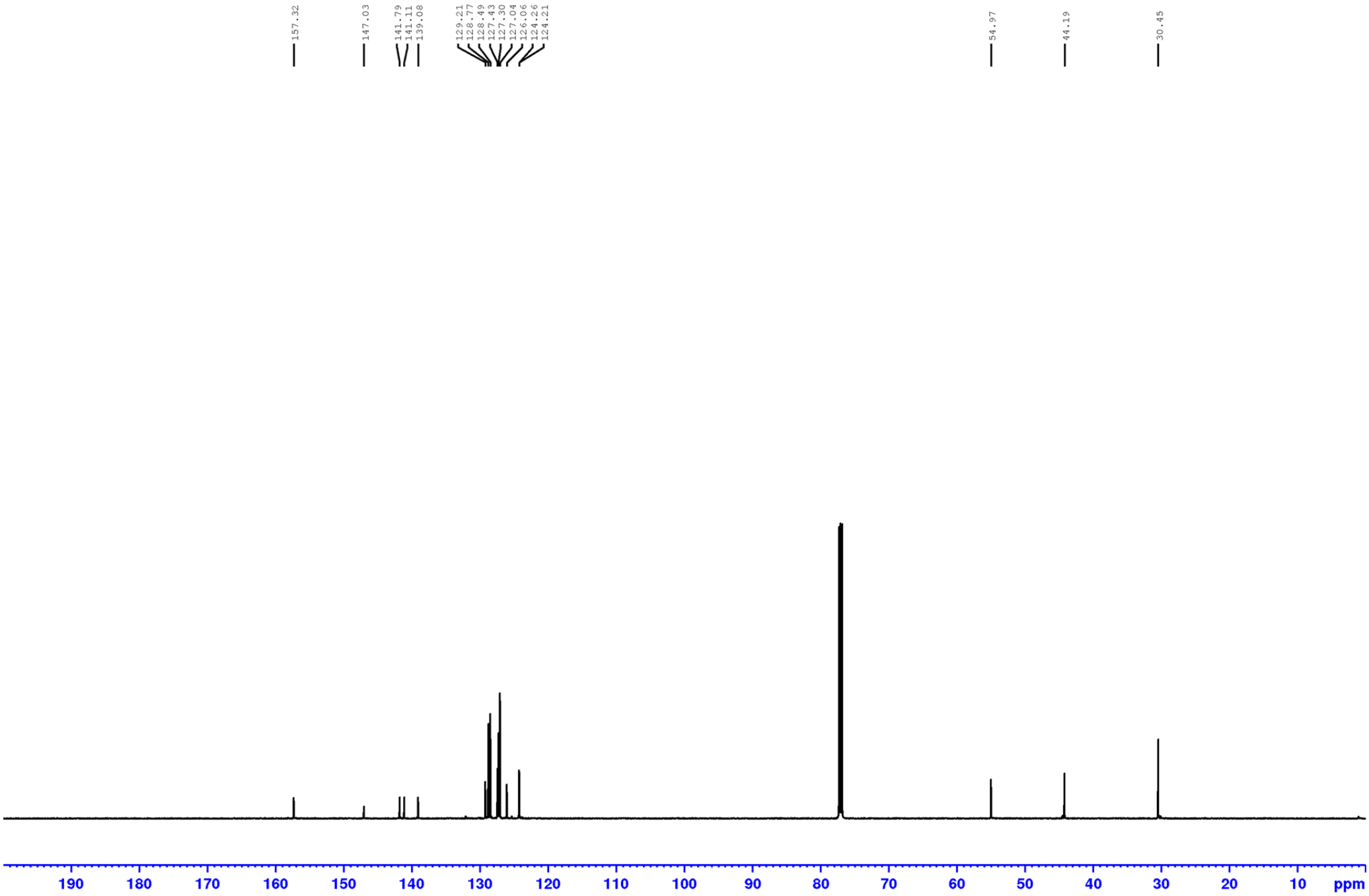
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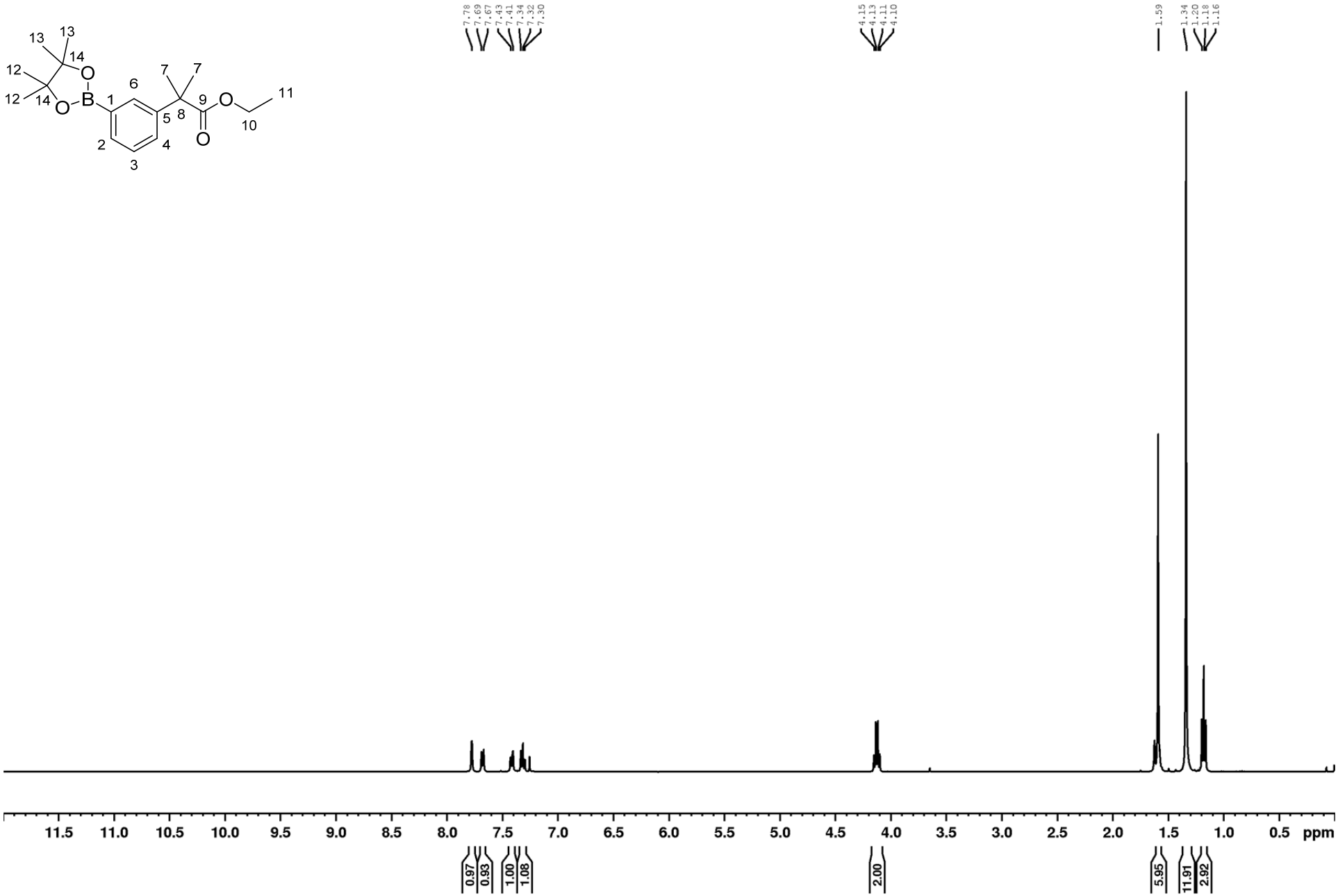


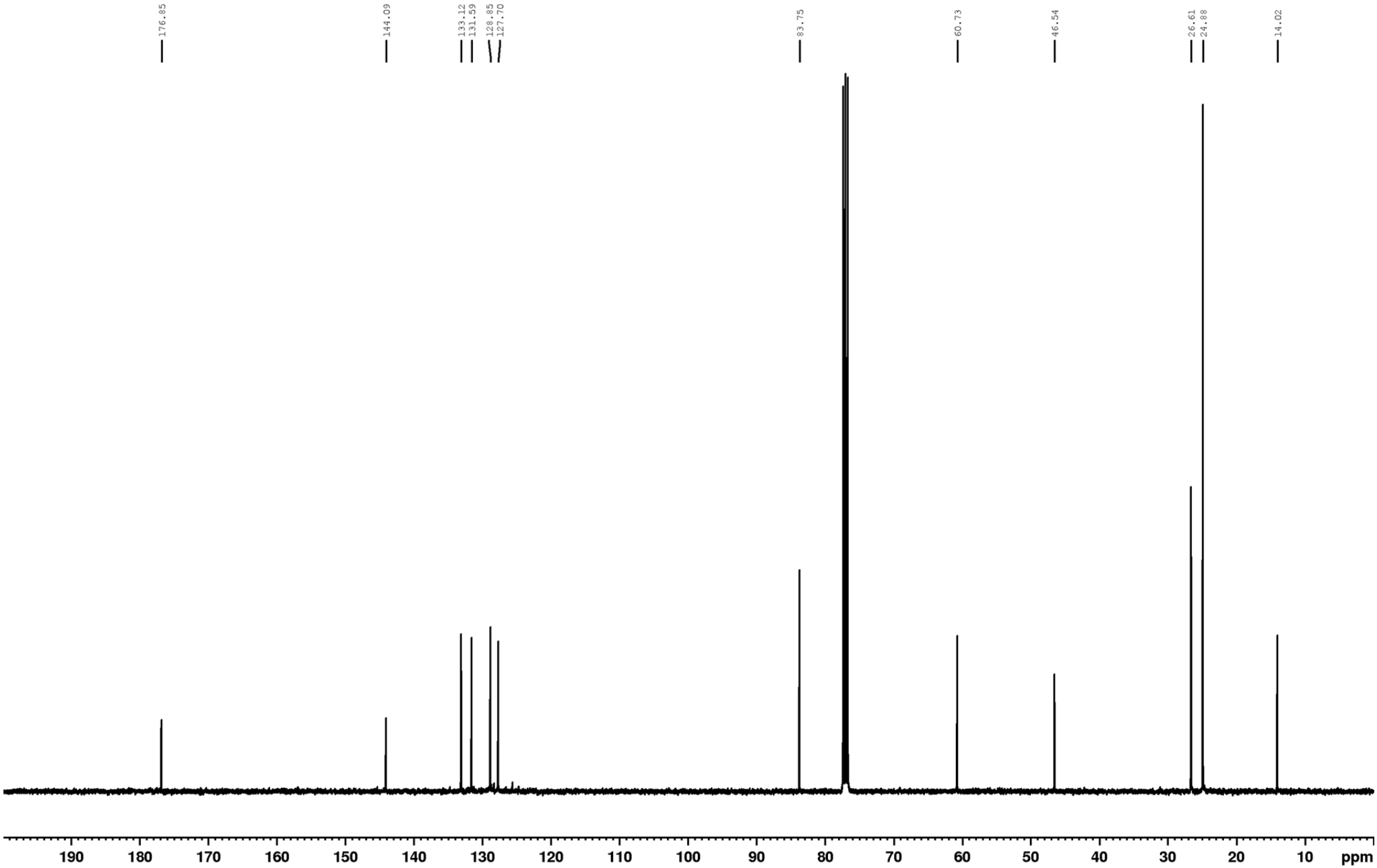




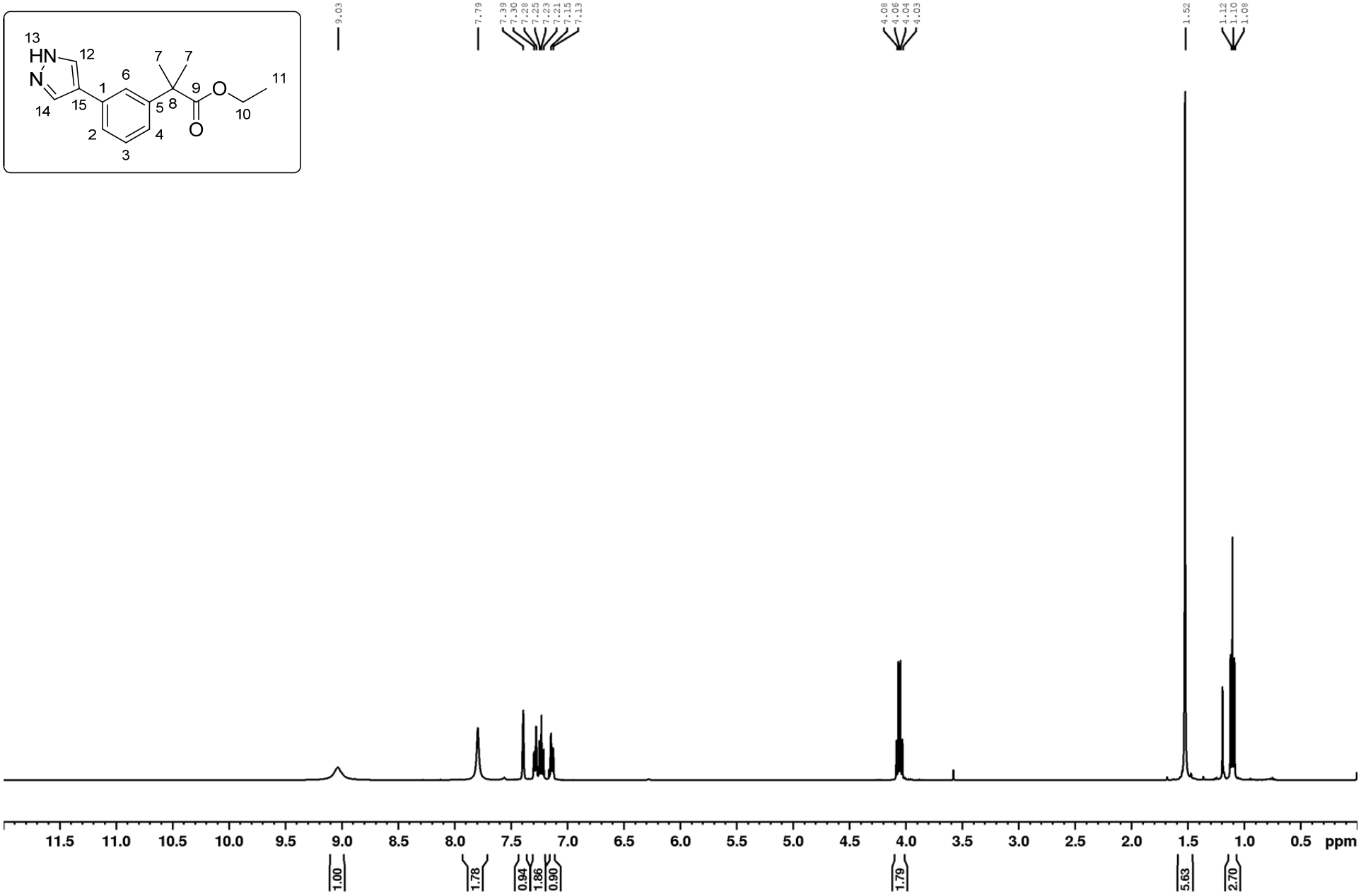

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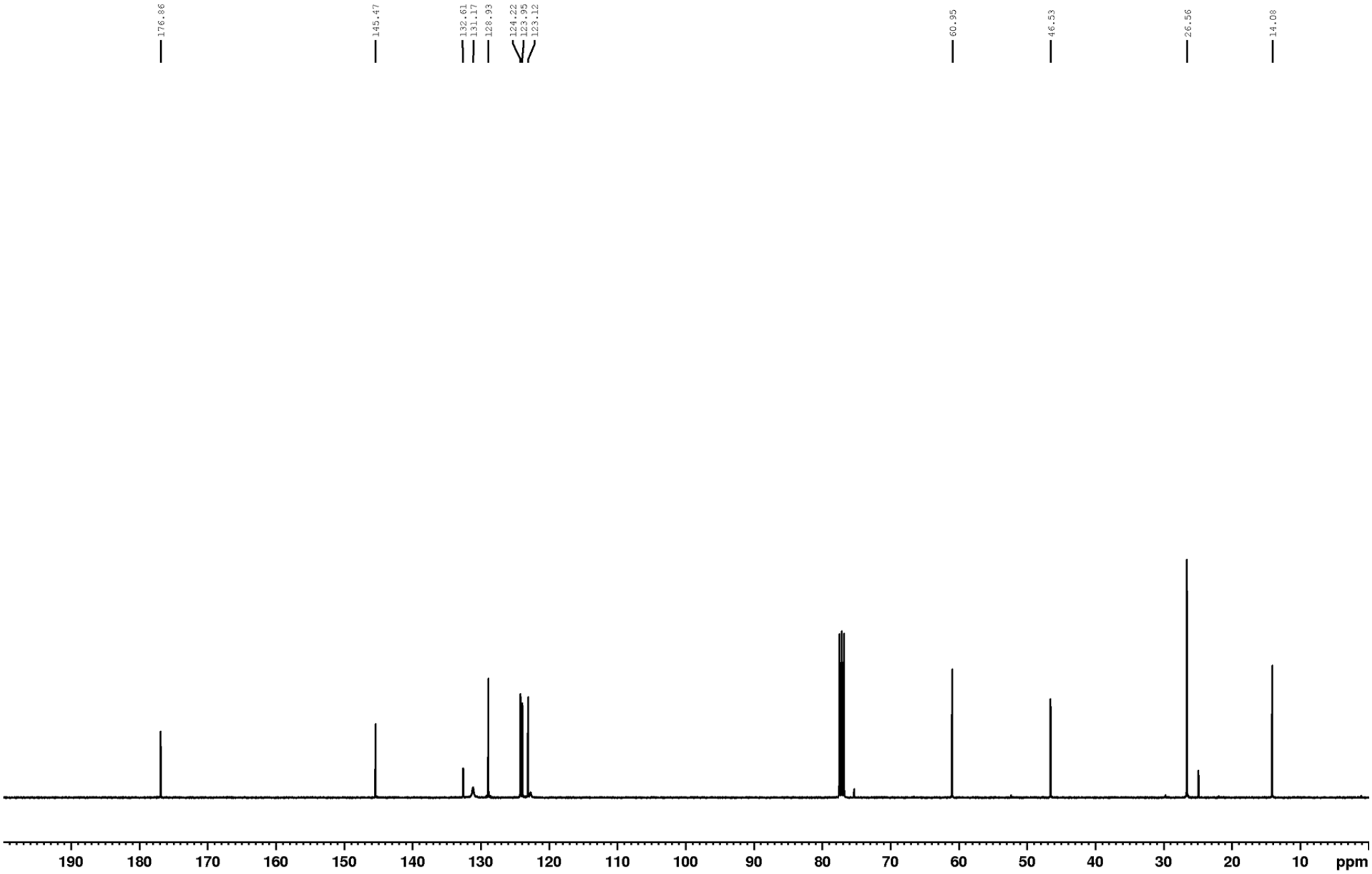
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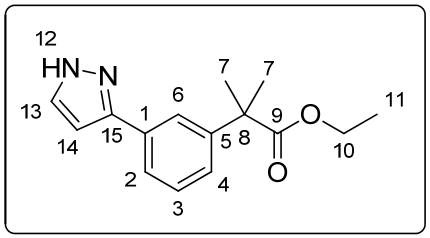

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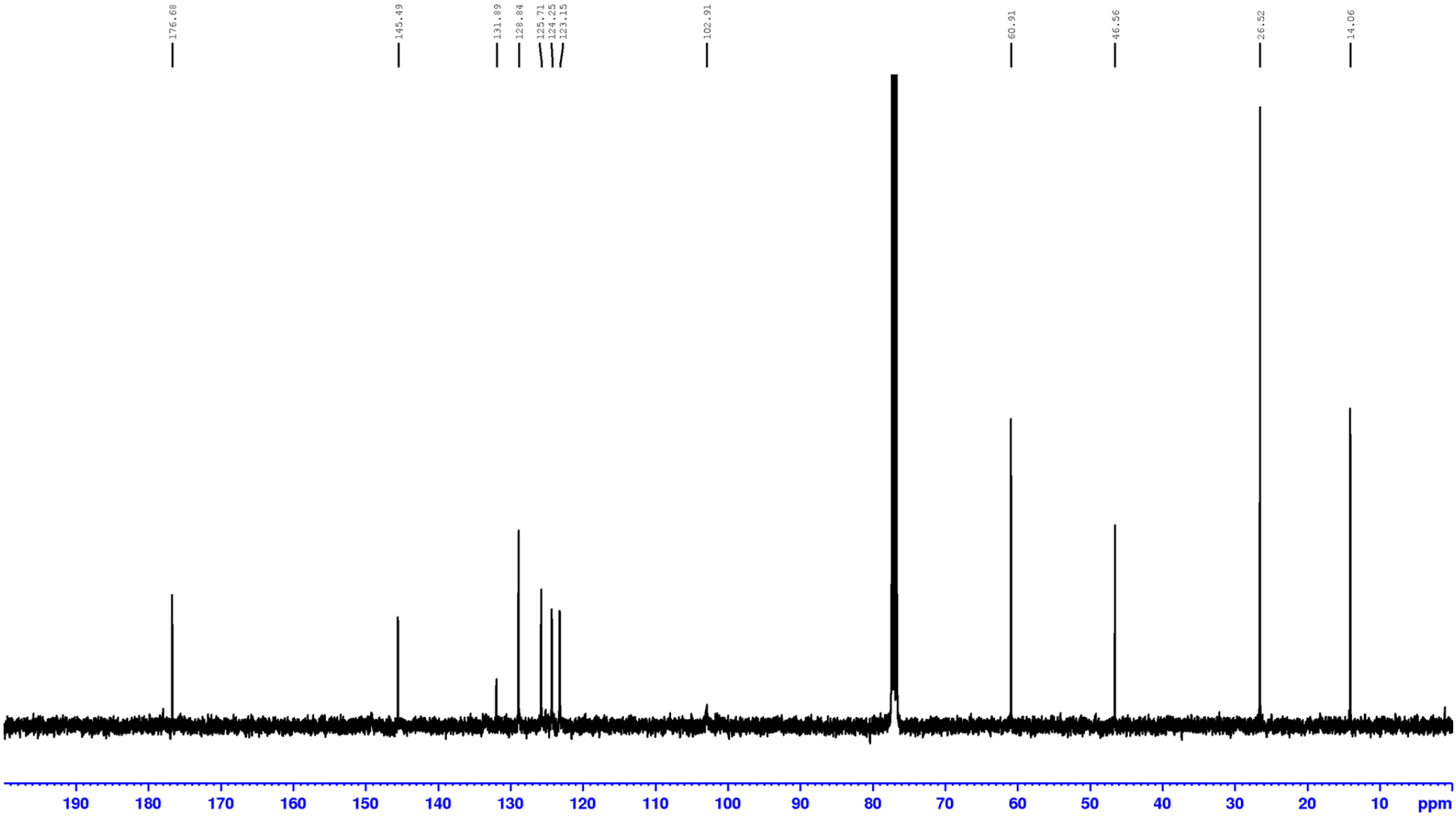
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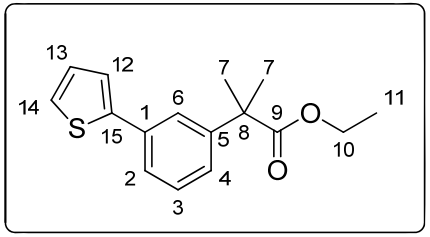

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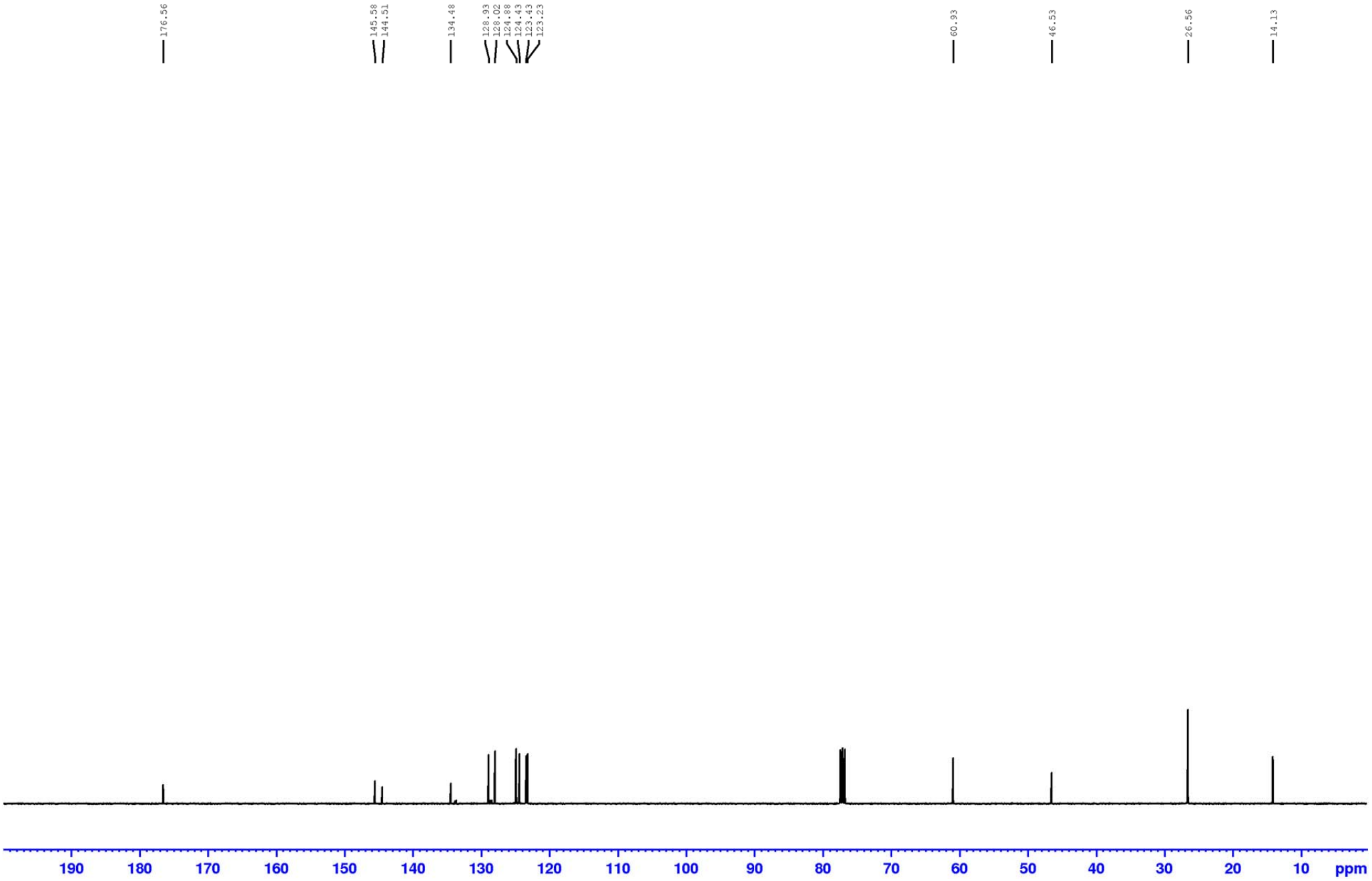
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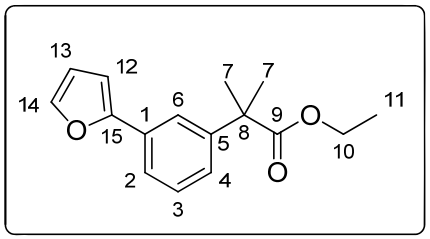

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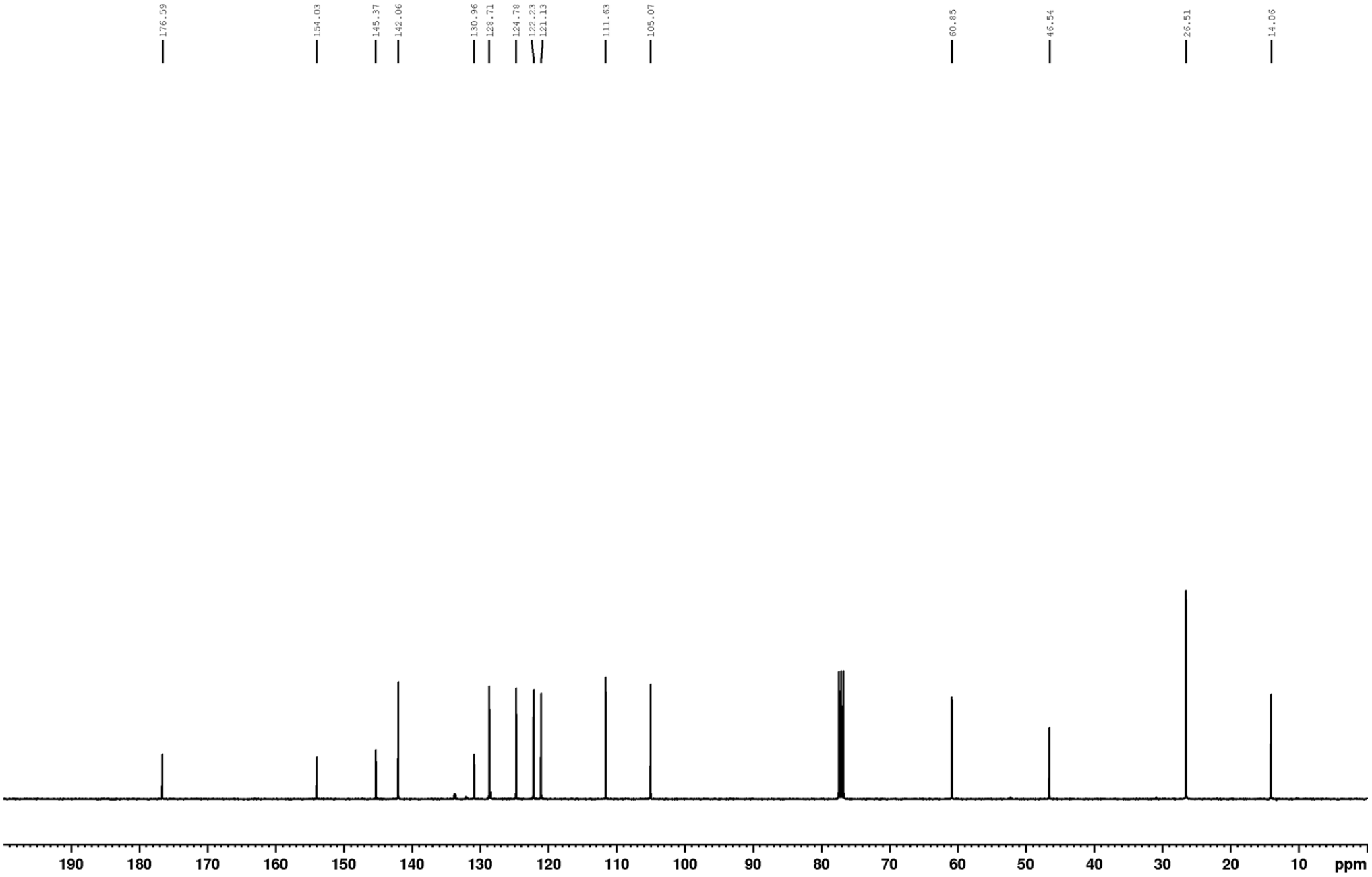
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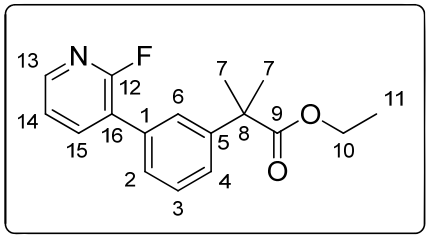

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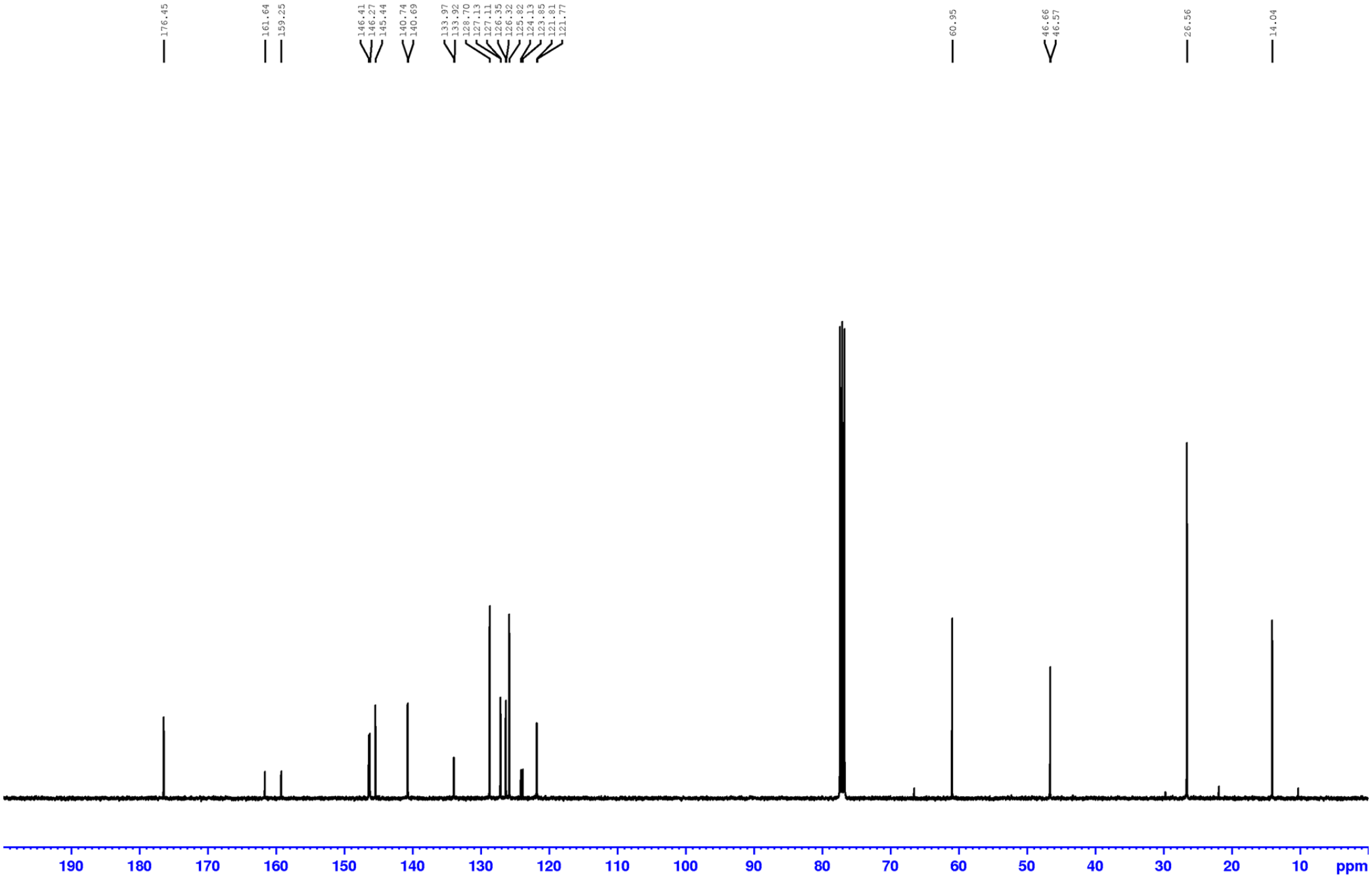
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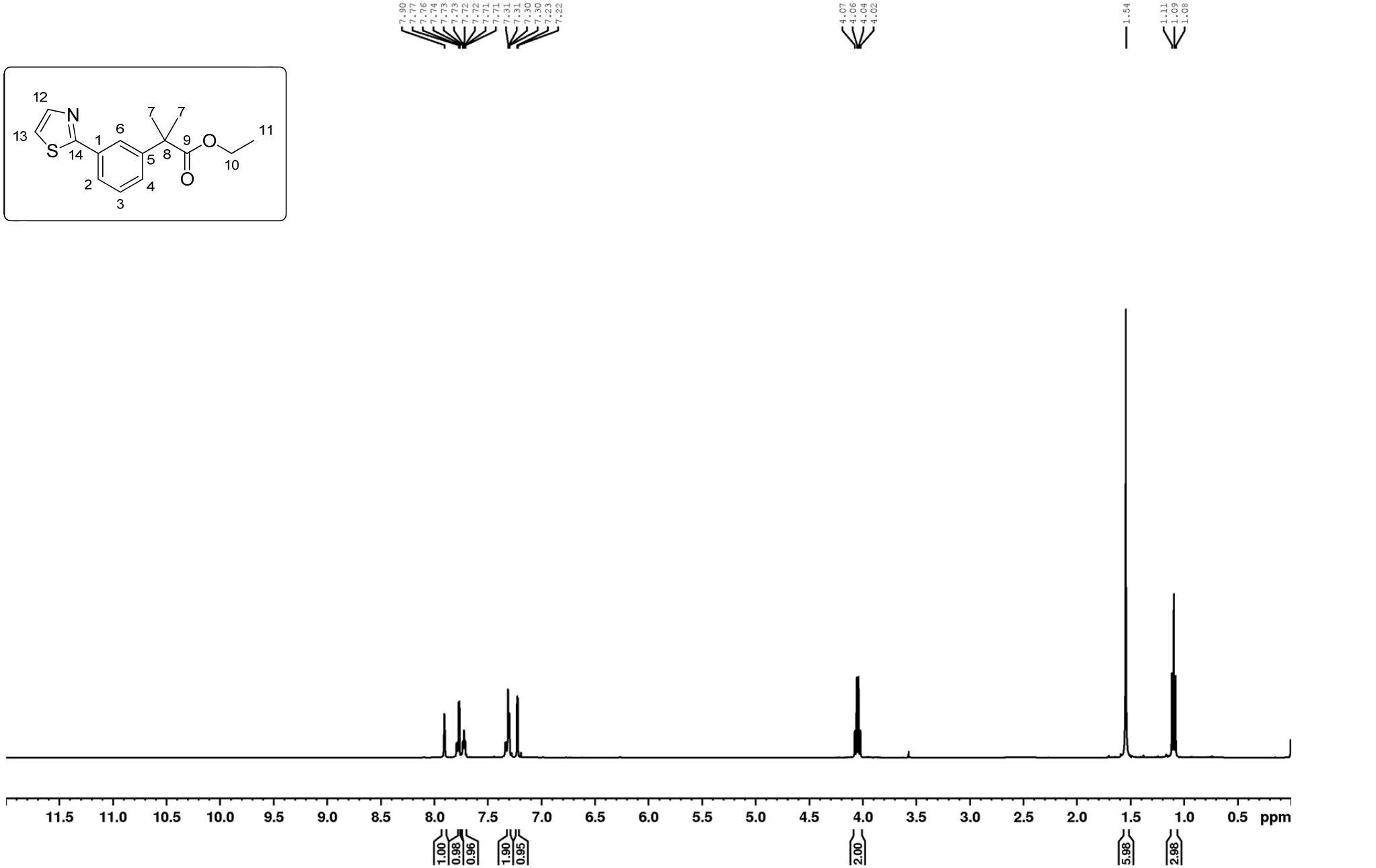

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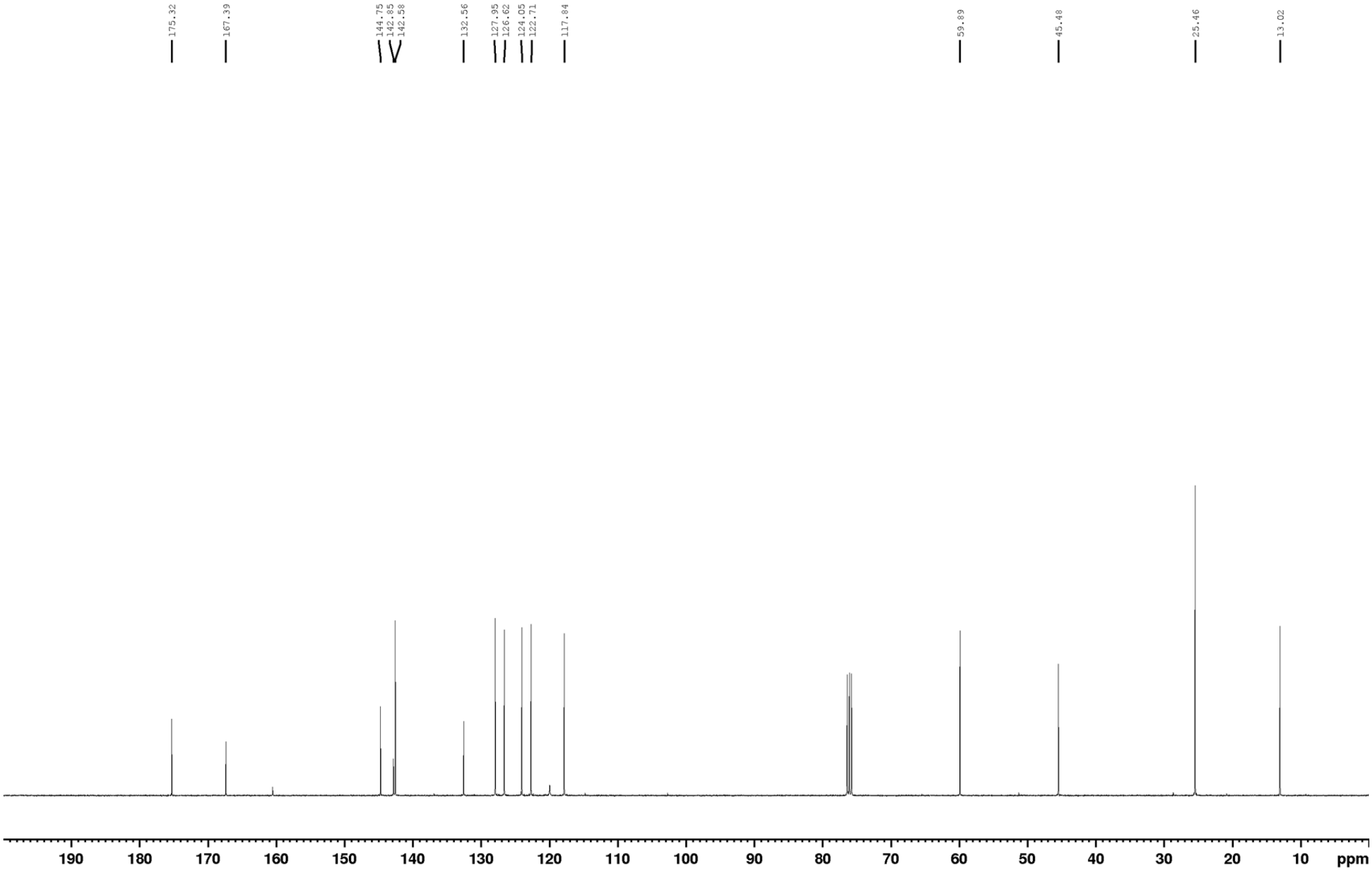
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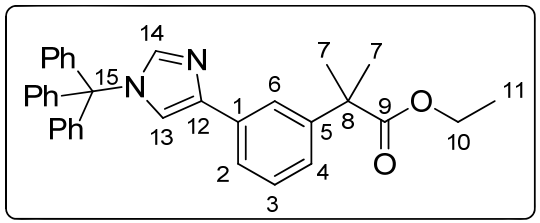

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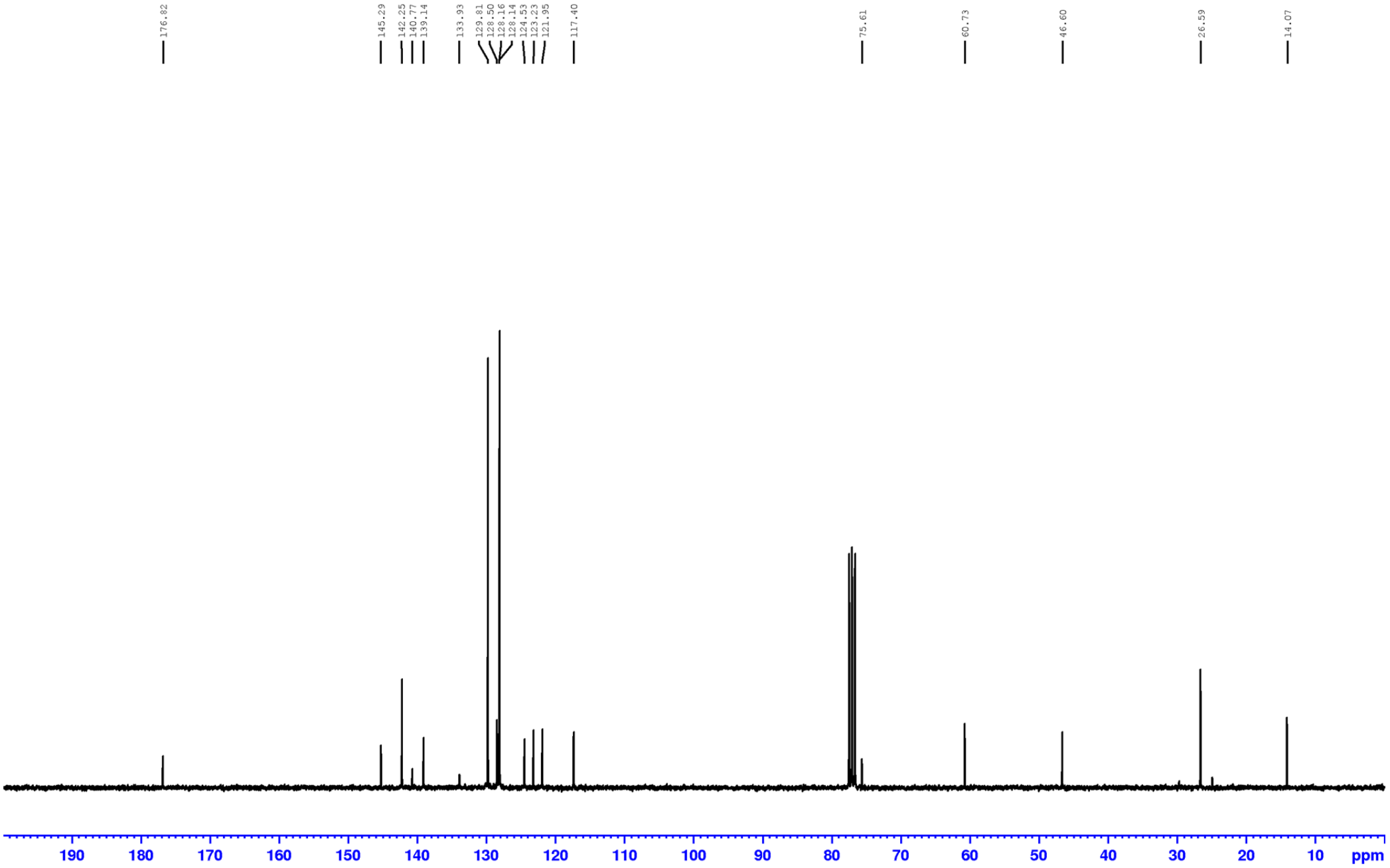
ethyl 2-methyl-2-(3-(thiazol-2-yl)phenyl)propanoate (21)



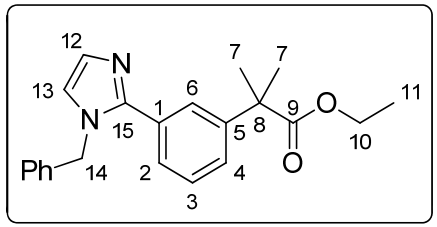

175.32
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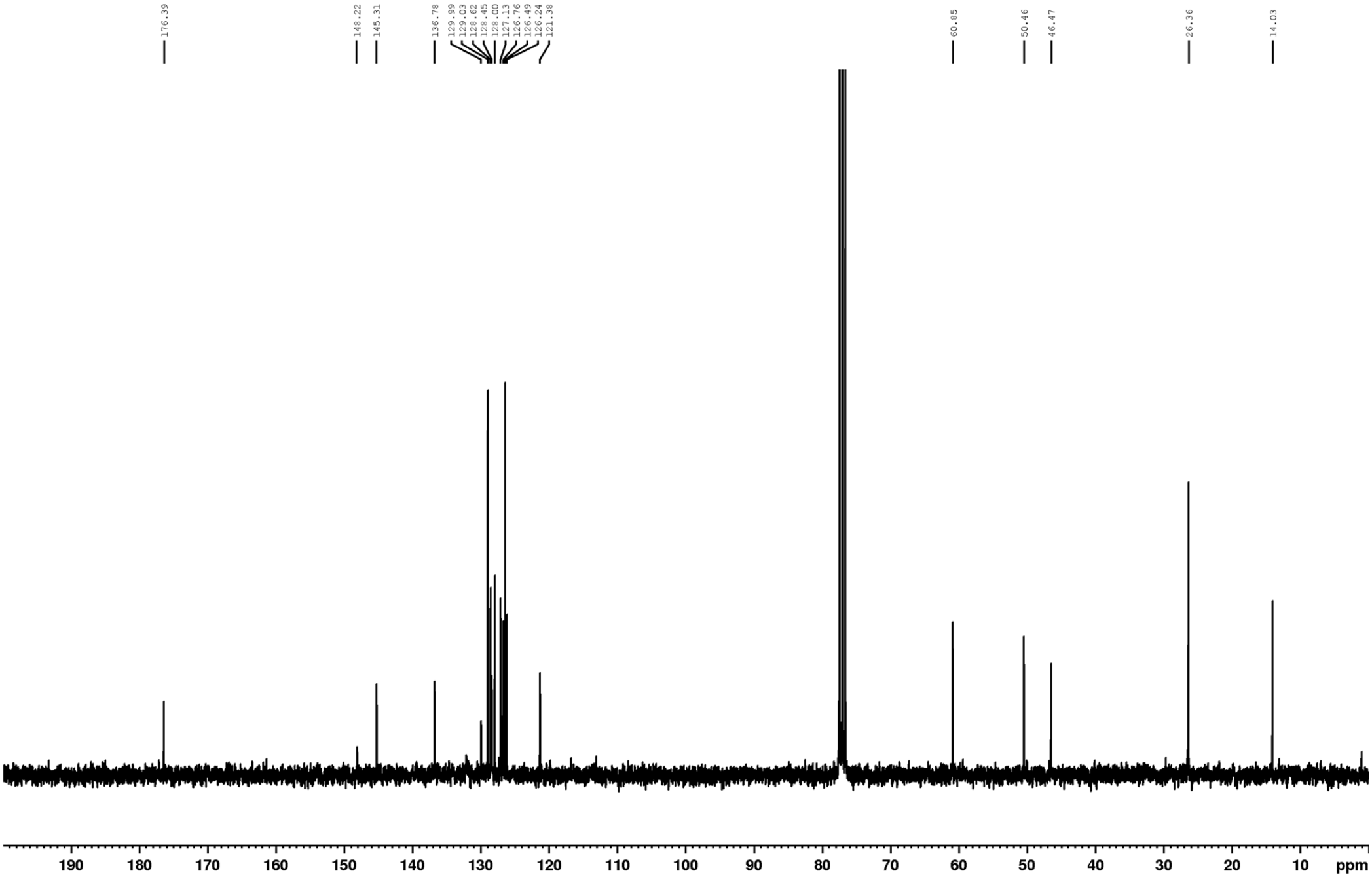
ethyl 2-methyl-2-(3-(1-trityl-1*H*-imidazol-4-yl)phenyl)propanoate (22)



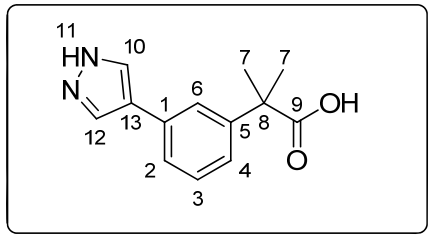

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117.40
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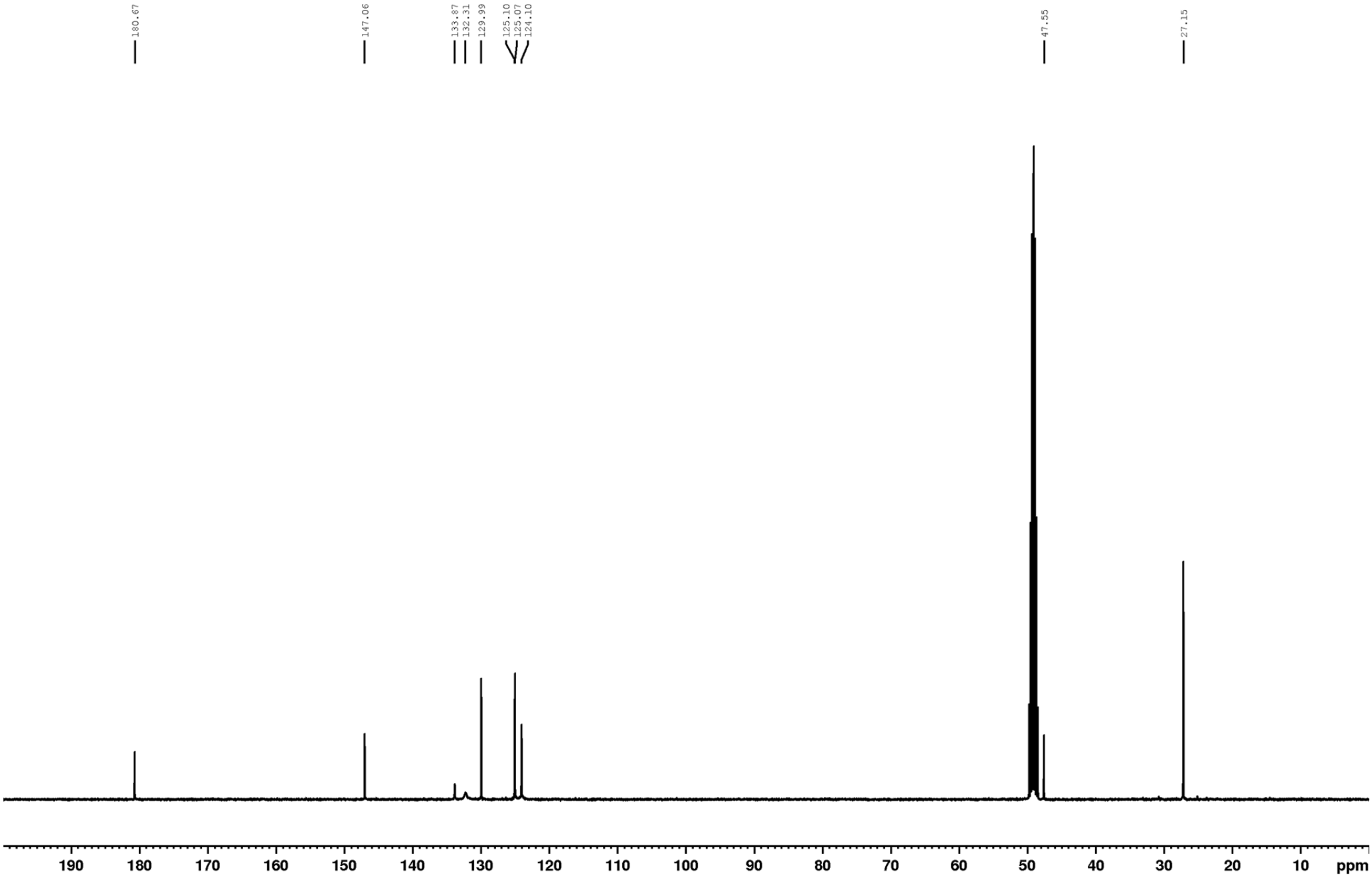
ethyl 2-(3-(1-benzyl-1*H*-imidazol-2-yl)phenyl)-2-methylpropanoate (23)



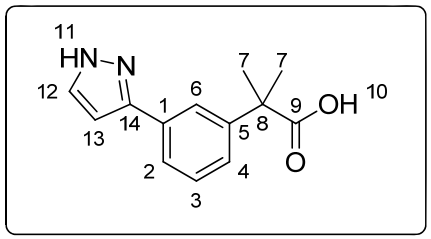

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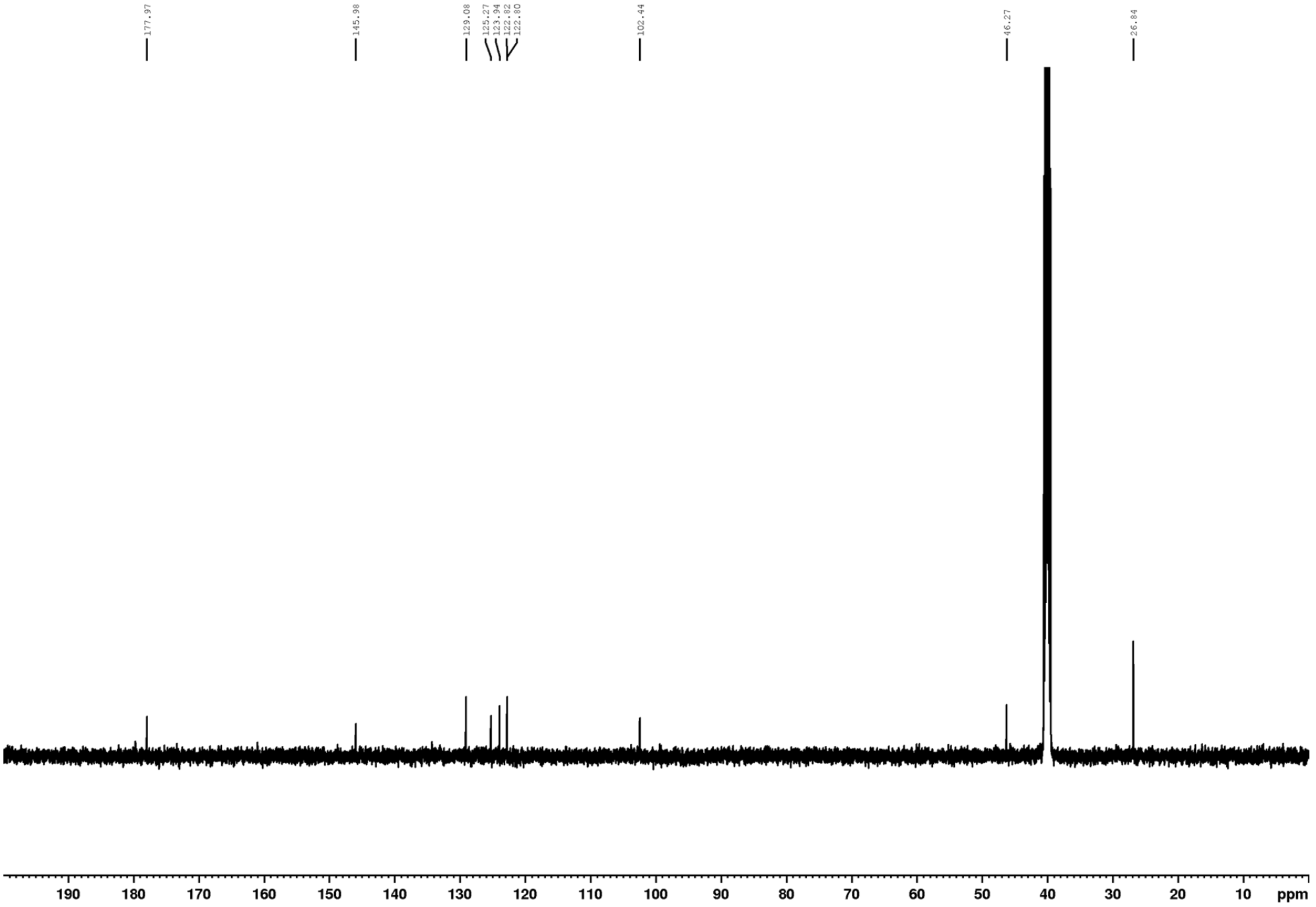
ethyl 2-(3-(1*H*-pyrazol-4-yl)phenyl)-2-methylpropanoate (24)



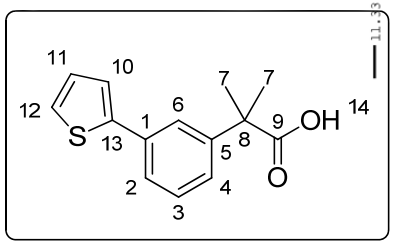

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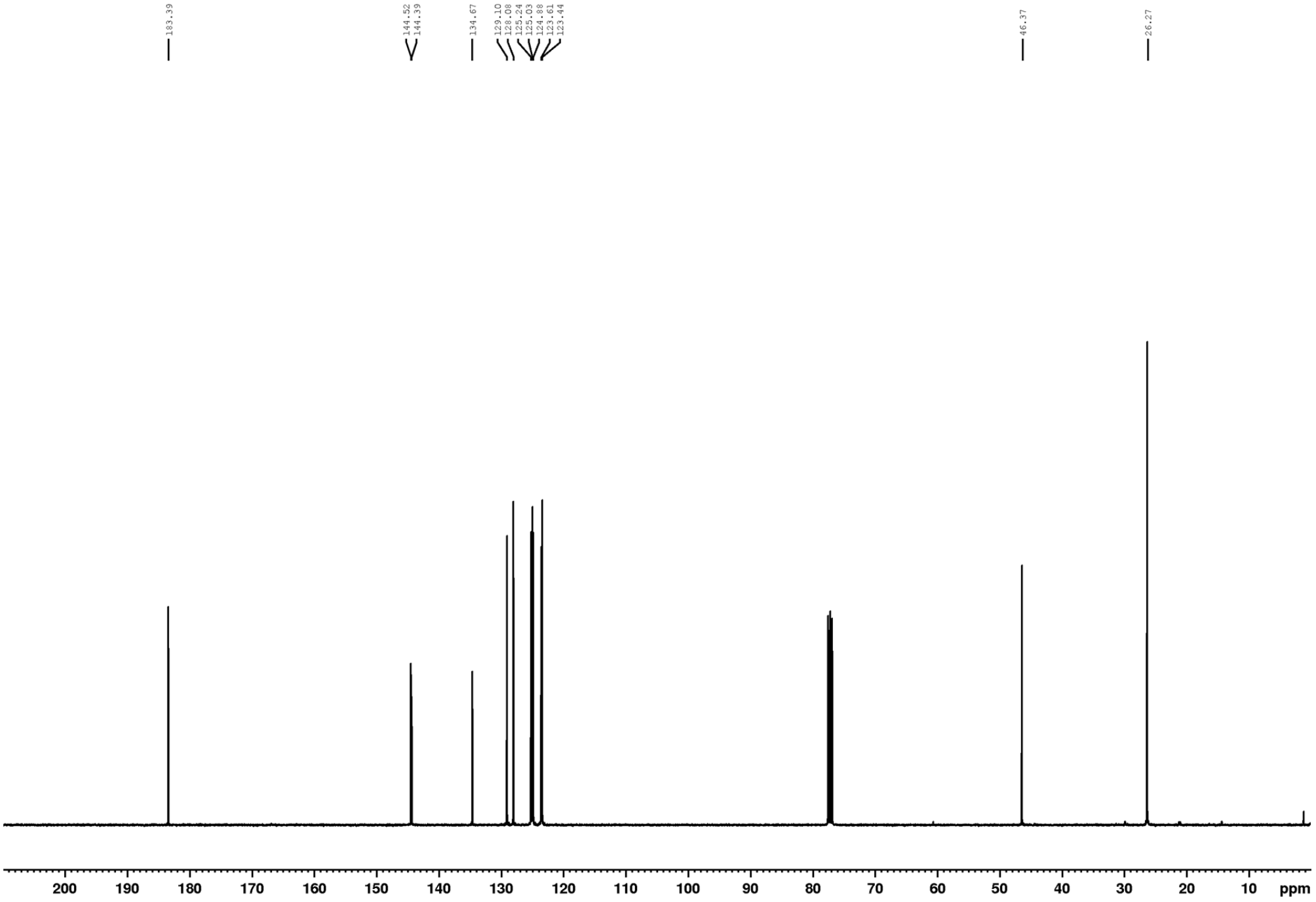
ethyl 2-(3-(1*H*-pyrazol-3-yl)phenyl)-2-methylpropanoate (25)



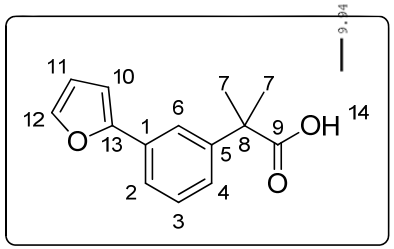

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102.44
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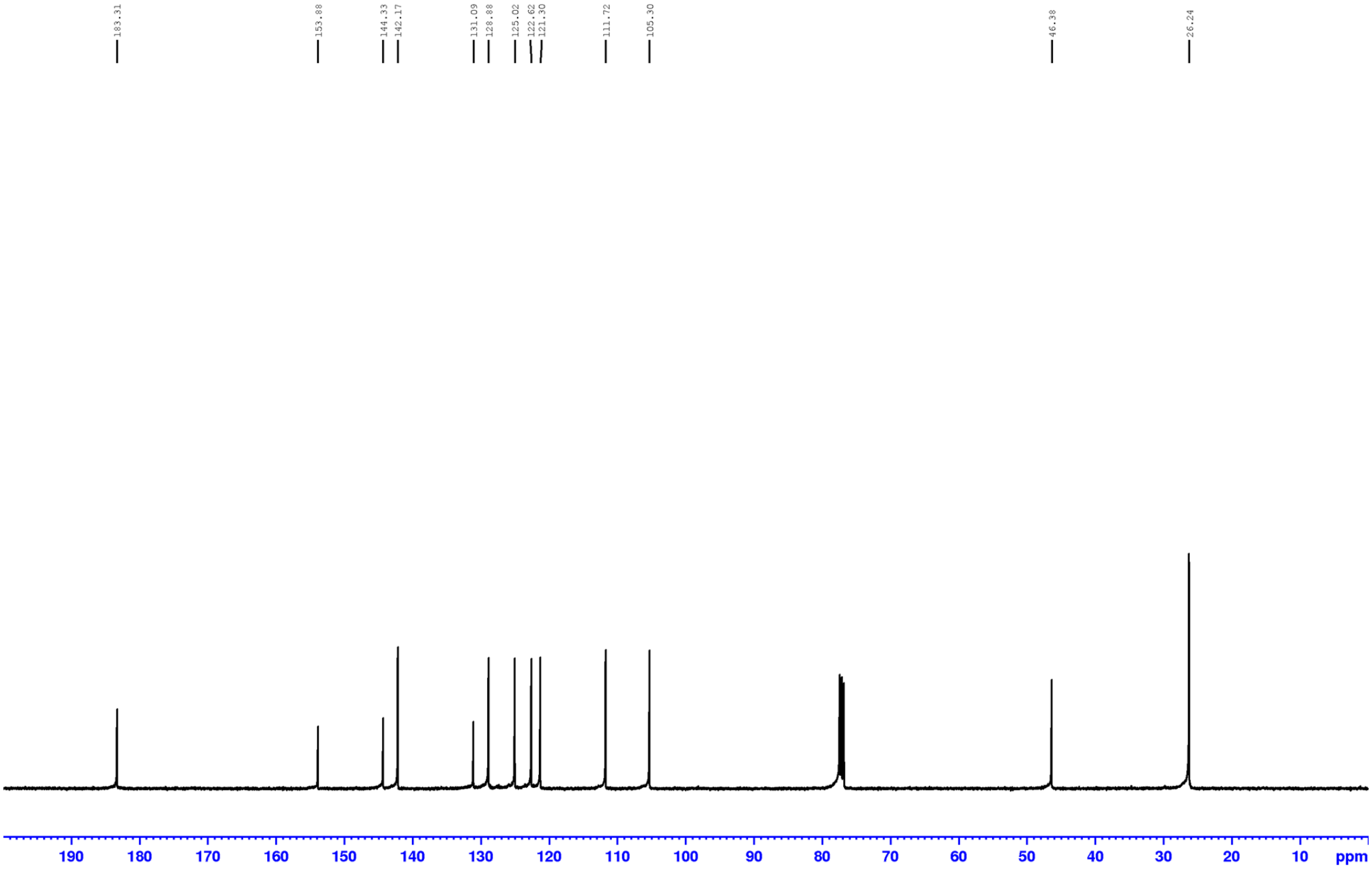
2-methyl-2-(3-(thiophen-2-yl)phenyl)propanoic acid (26)



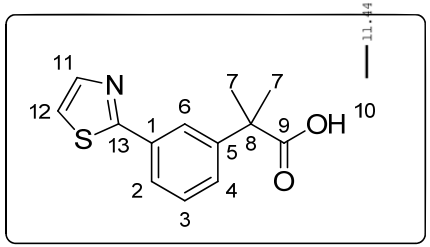

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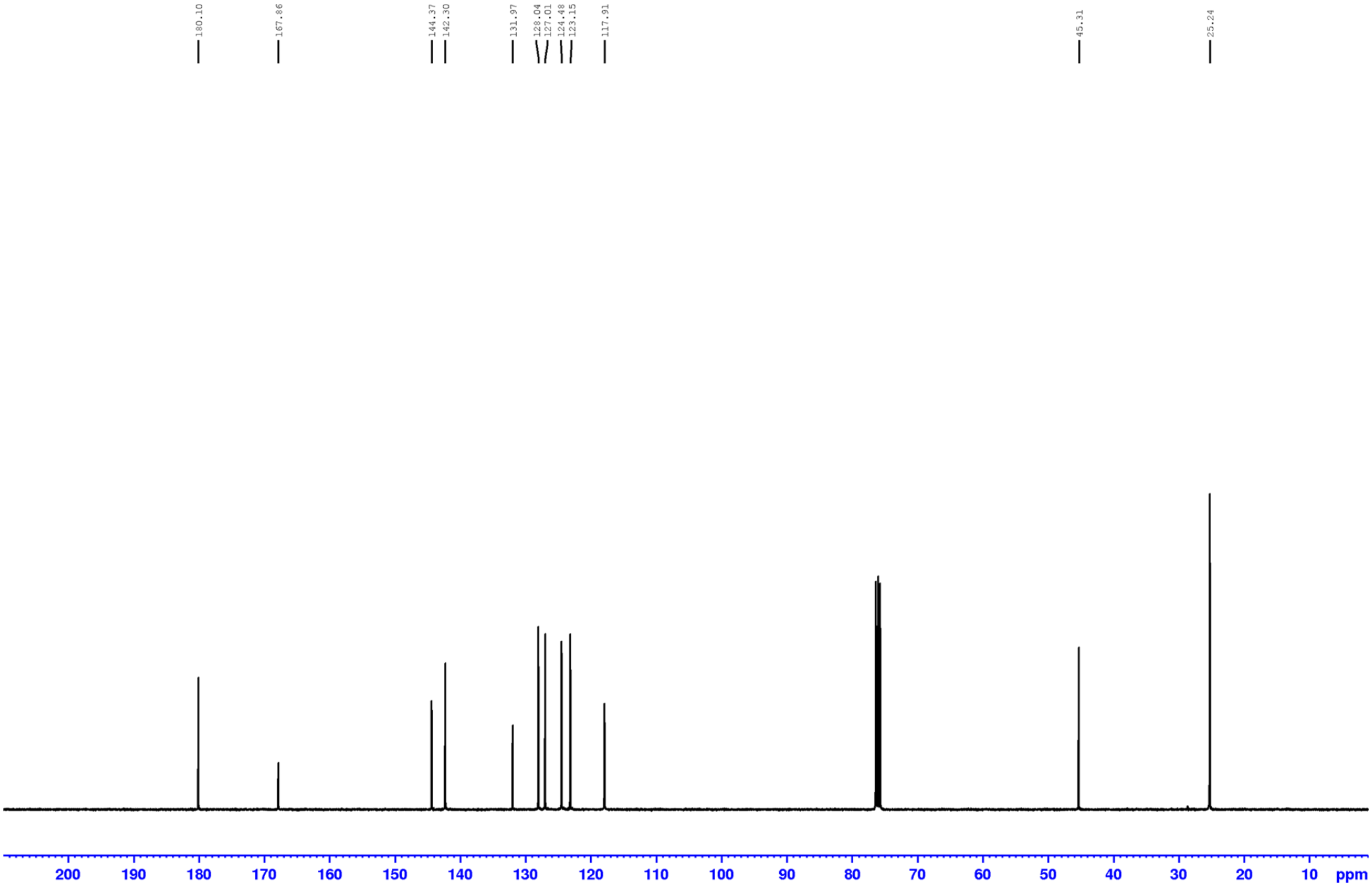
2-(3-(furan-2-yl)phenyl)-2-methylpropanoic acid (27)



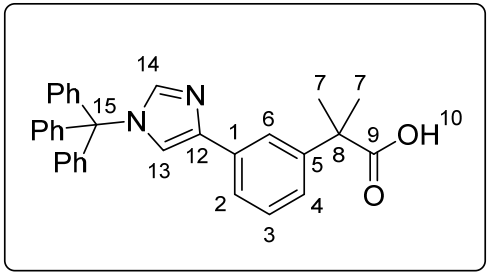

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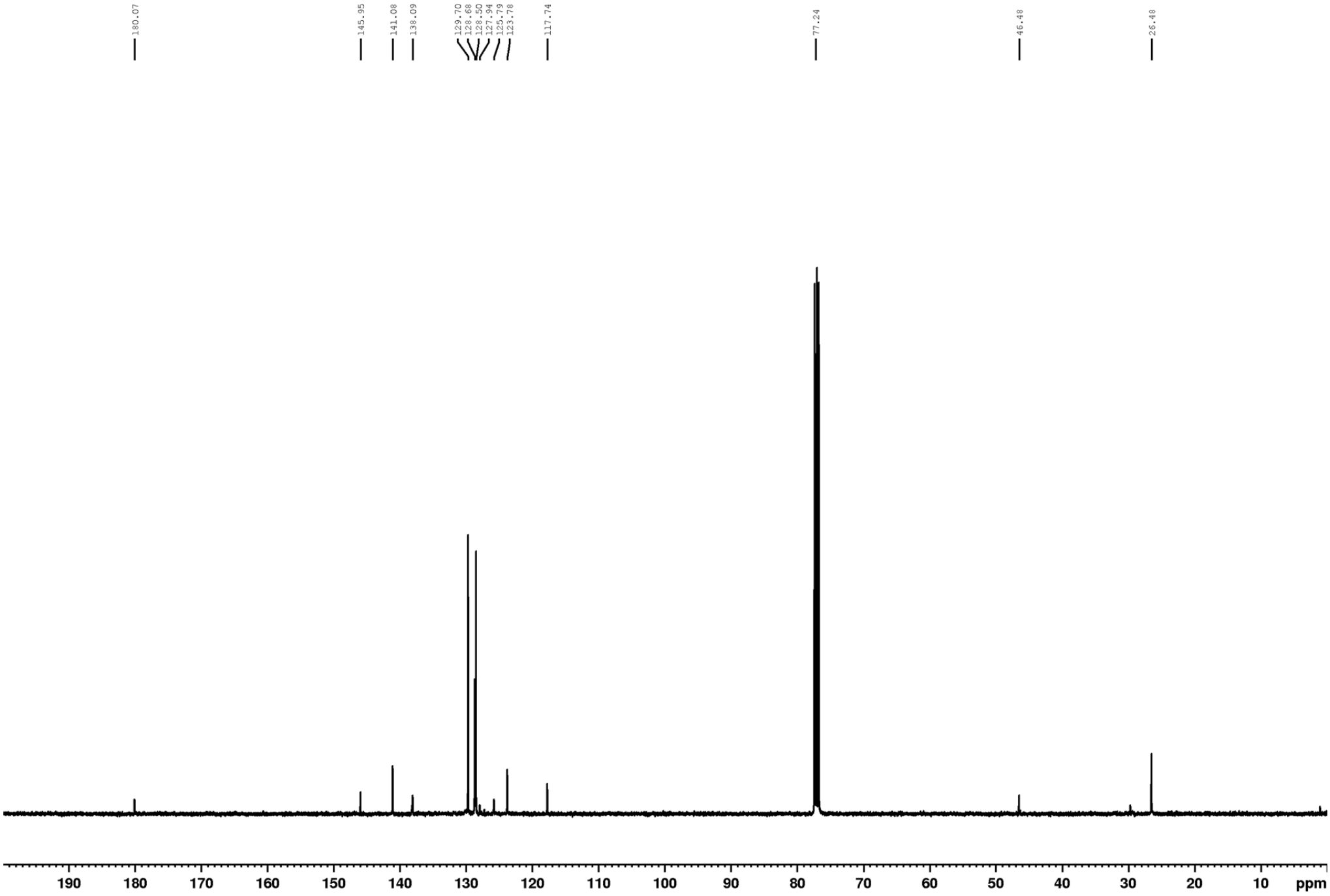
2-methyl-2-(3-(thiazol-2-yl)phenyl)propanoic acid (28)



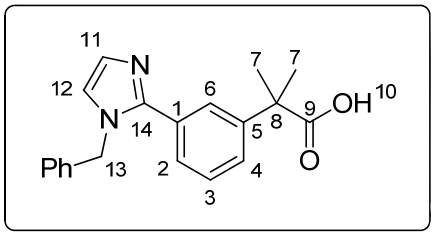

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127.01
124.48
123.15
117.91
45.31
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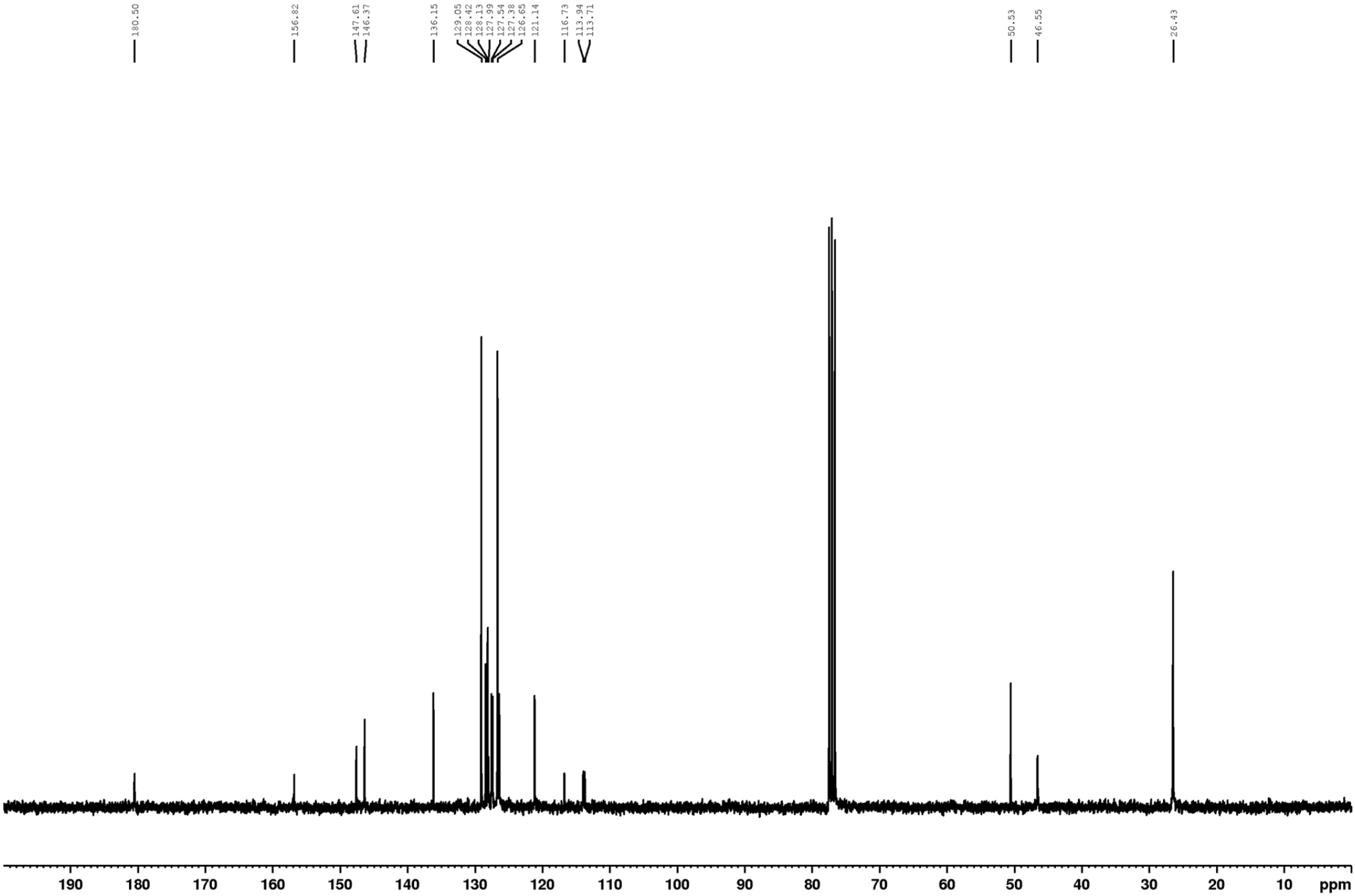
2-methyl-2-(3-(1-trityl-1*H*-imidazol-4-yl)phenyl)propanoic acid (29)



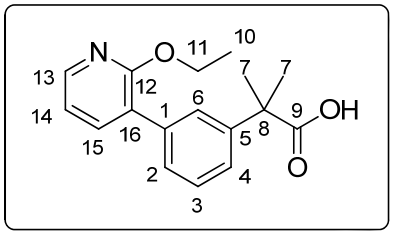

180.07
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128.50
127.94
125.79
123.78
117.74
77.24
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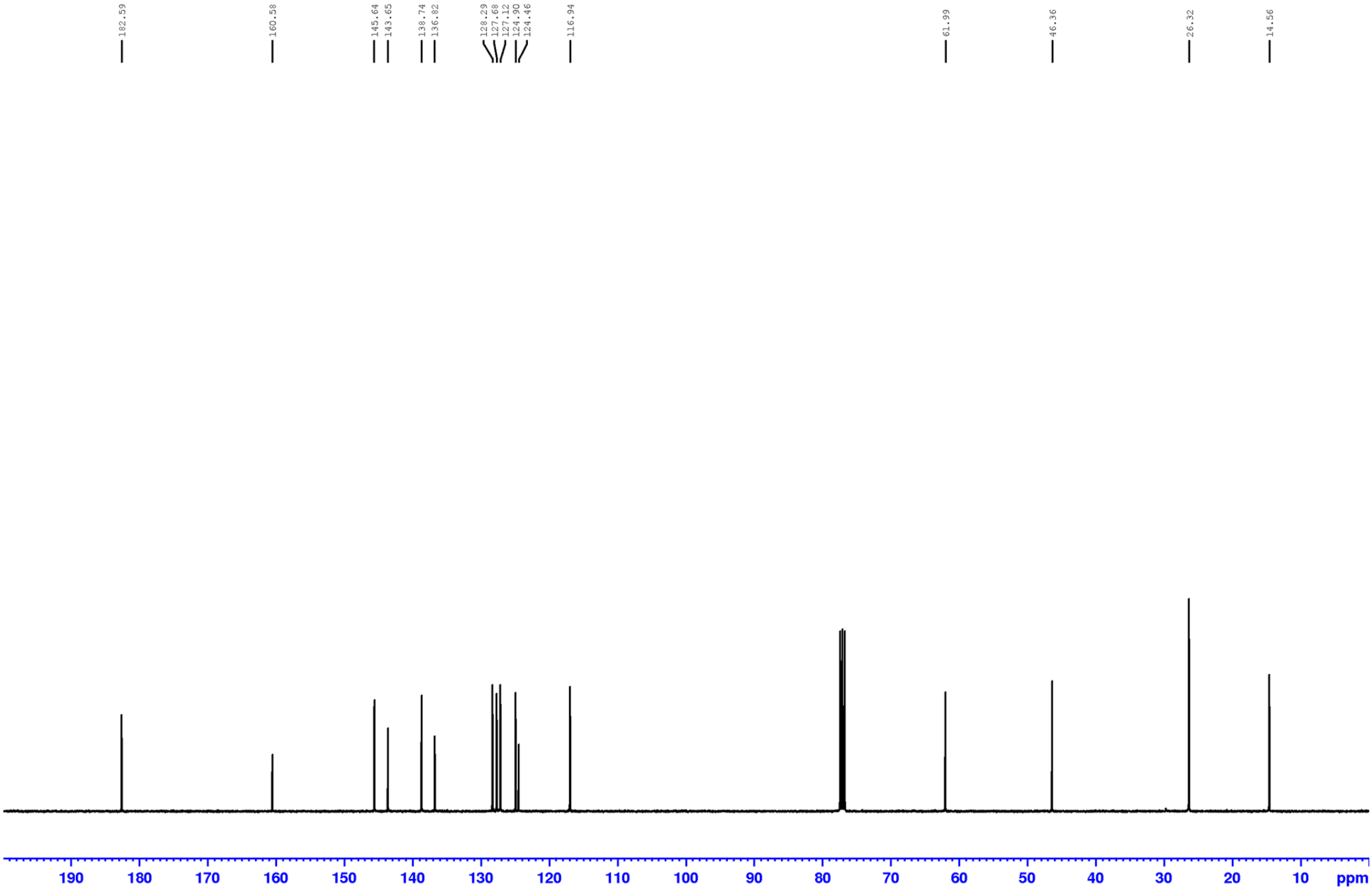
2-(3-(1-benzyl-1*H*-imidazol-2-yl)phenyl)-2-methylpropanoic acid (30)



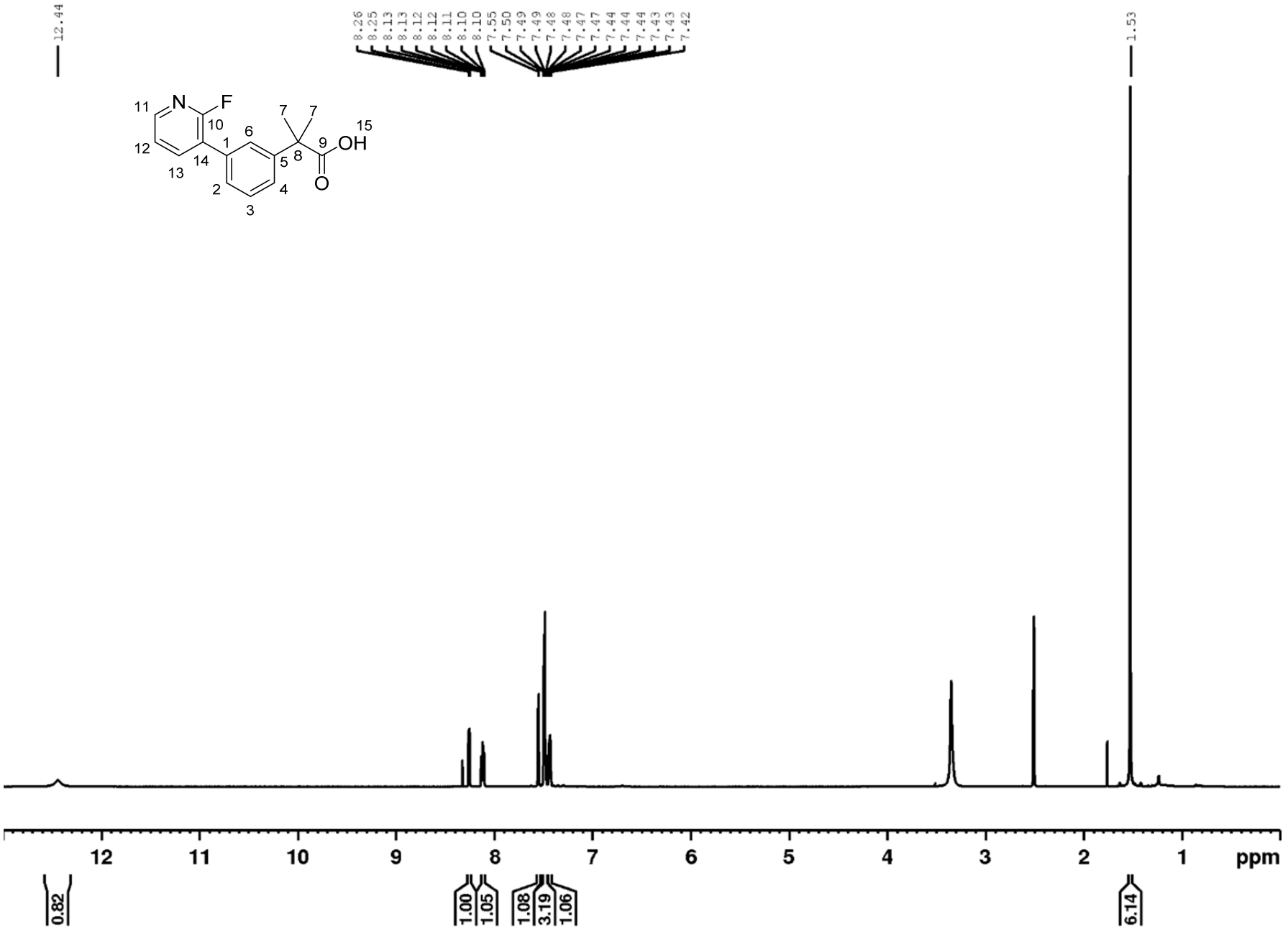

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113.94
113.71
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46.55
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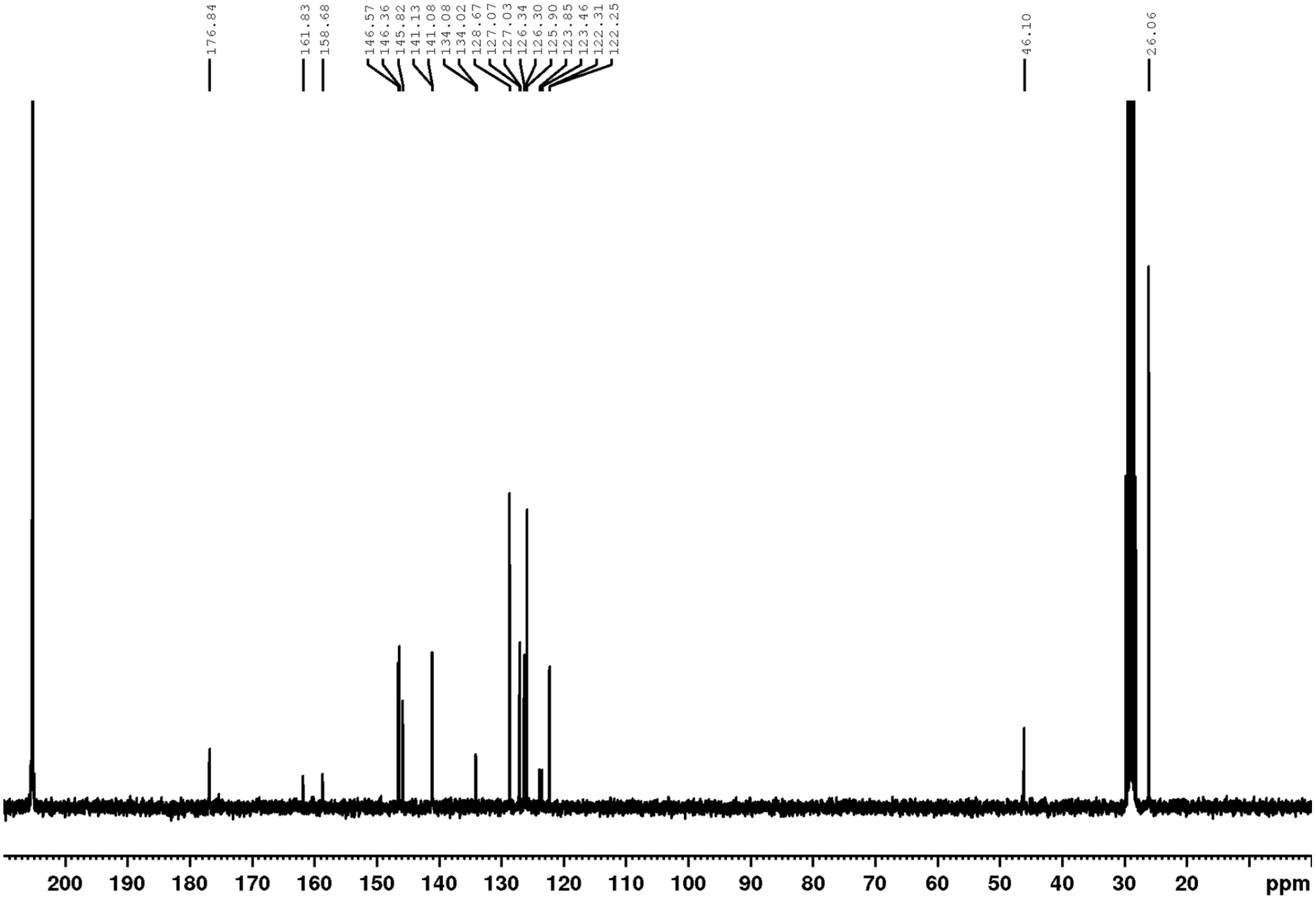
2-(3-(2-ethoxypyridin-3-yl)phenyl)-2-methylpropanoic acid (31)



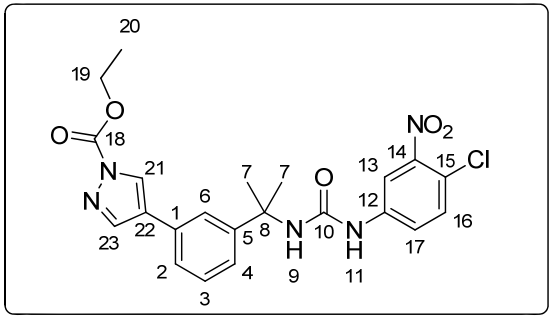

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116.94
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26.32
14.56
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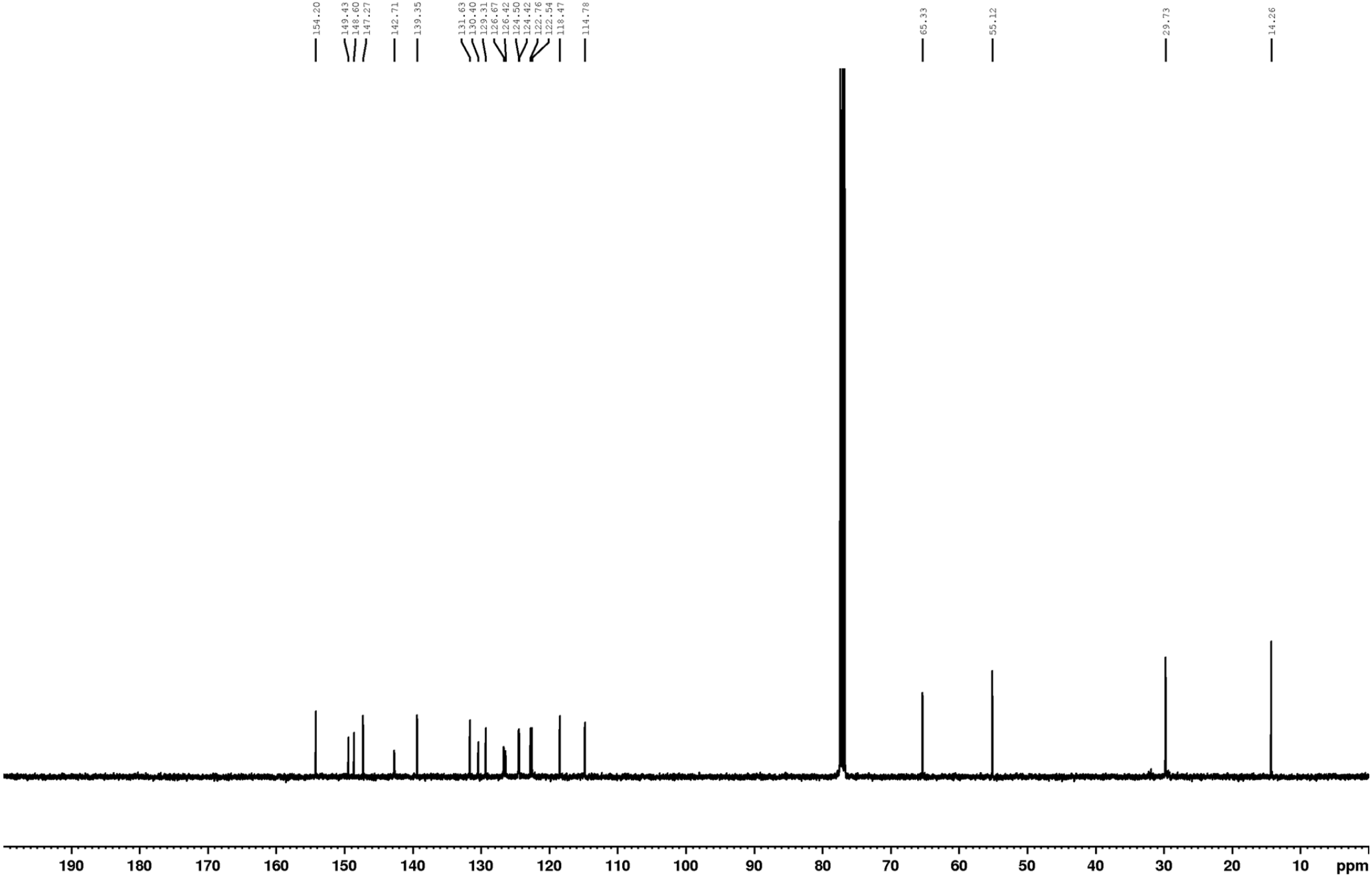
2-(3-(2-fluoropyridin-3-yl)phenyl)-2-methylpropanoic acid (32)



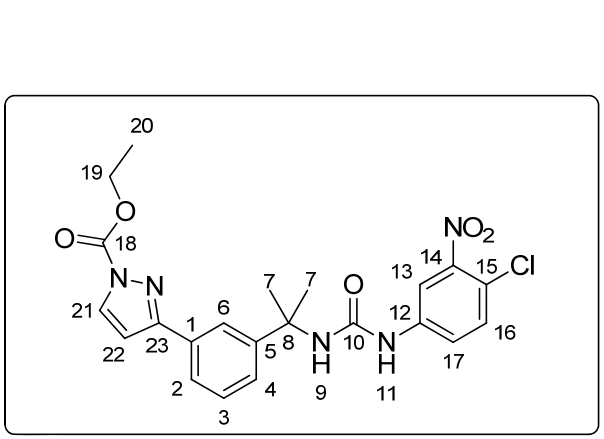

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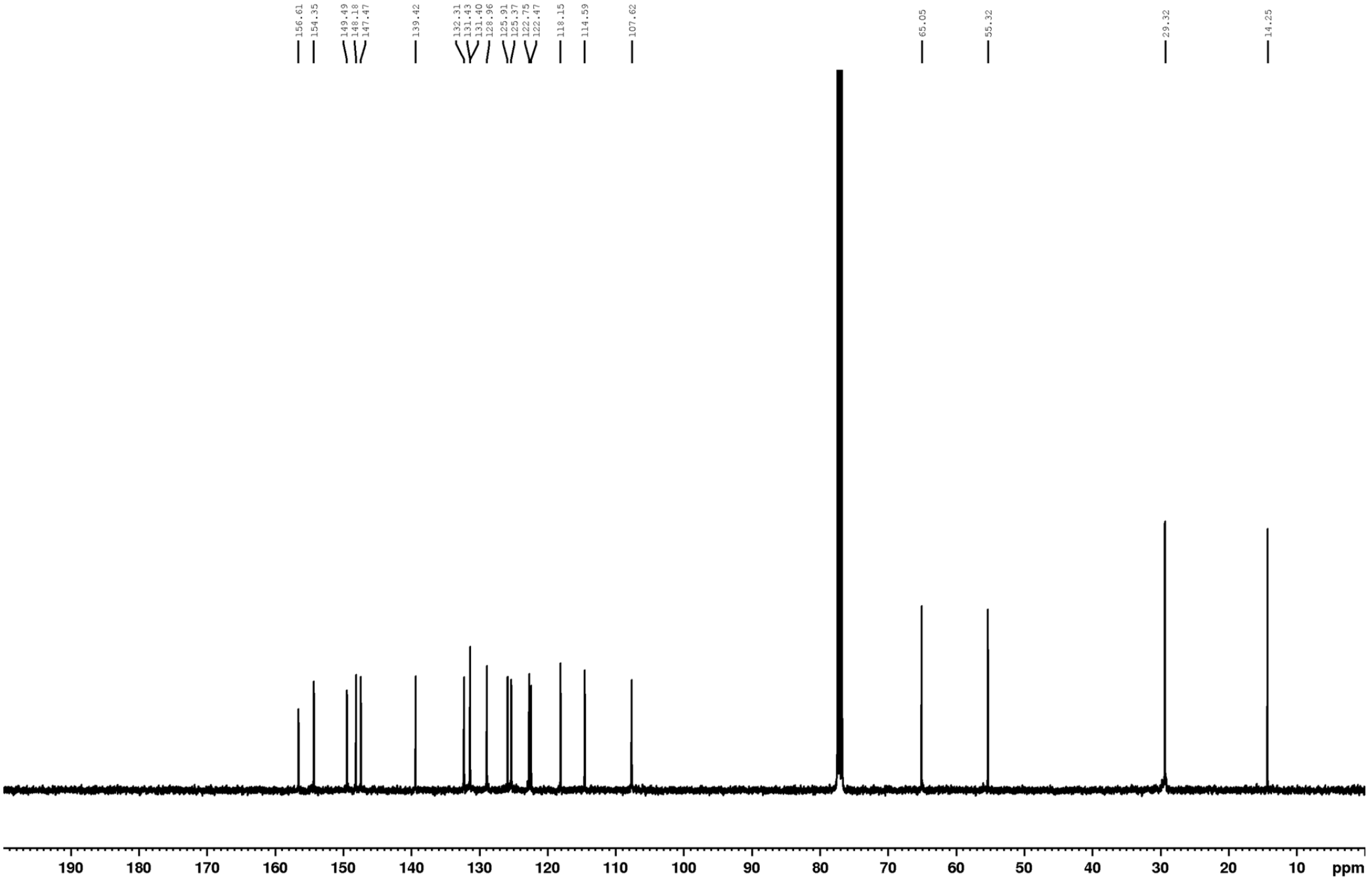
ethyl 4-(3-(2-(3-(4-chloro-3-nitrophenyl)ureido)propan-2-yl)phenyl)-1*H*-pyrazole-1-carboxylate (33)



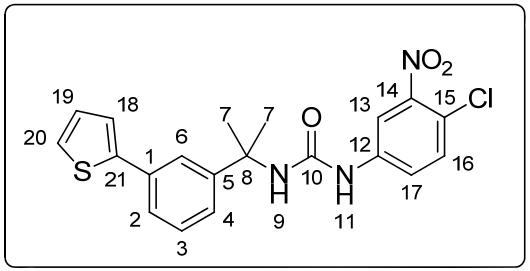

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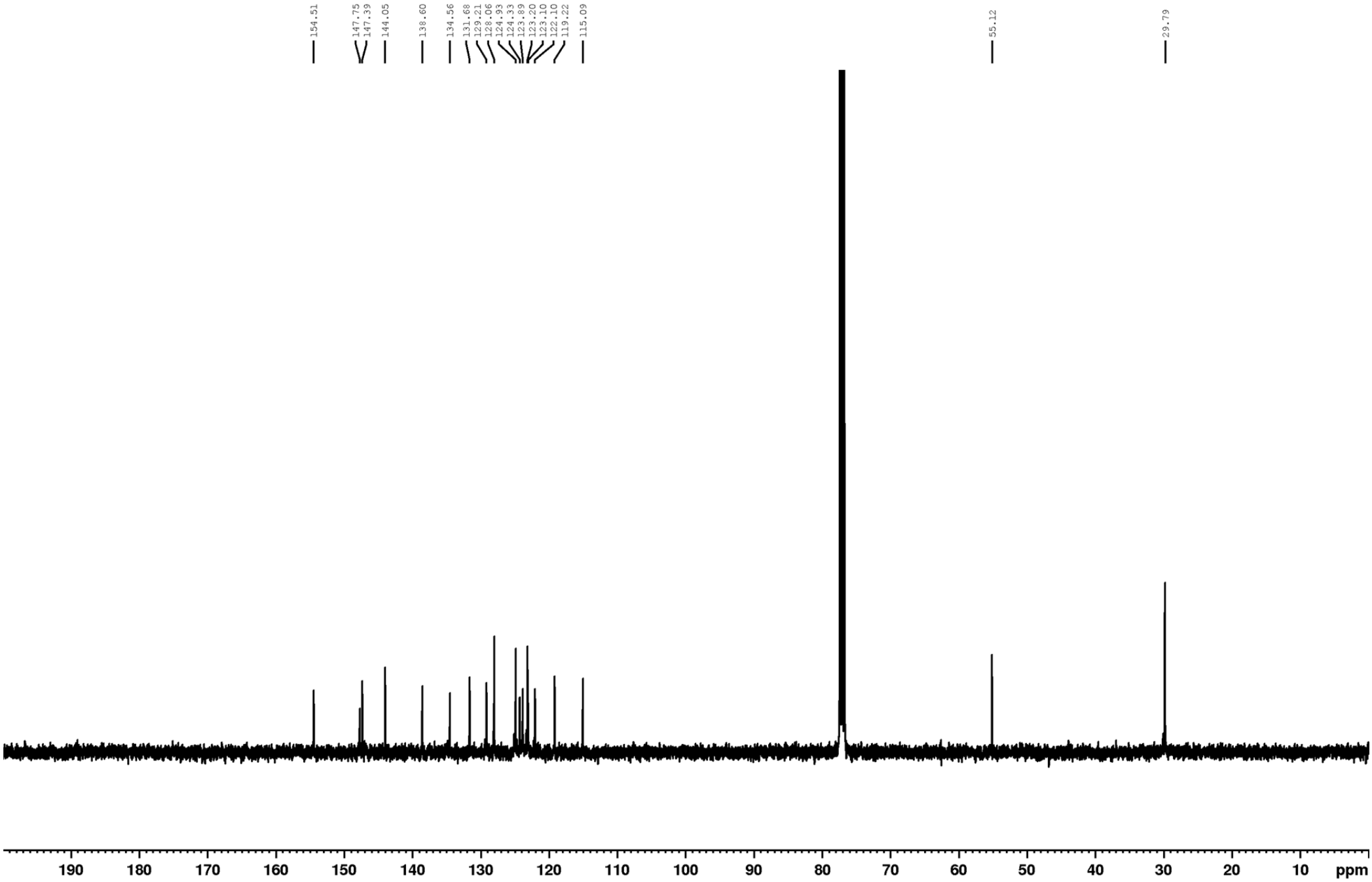
ethyl 3-(3-(2-(3-(4-chloro-3-nitrophenyl)ureido)propan-2-yl)phenyl)-1*H*-pyrazole-1-carboxylate (34)



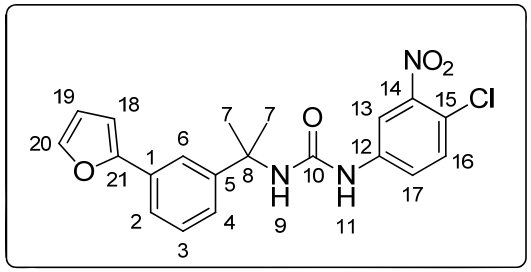

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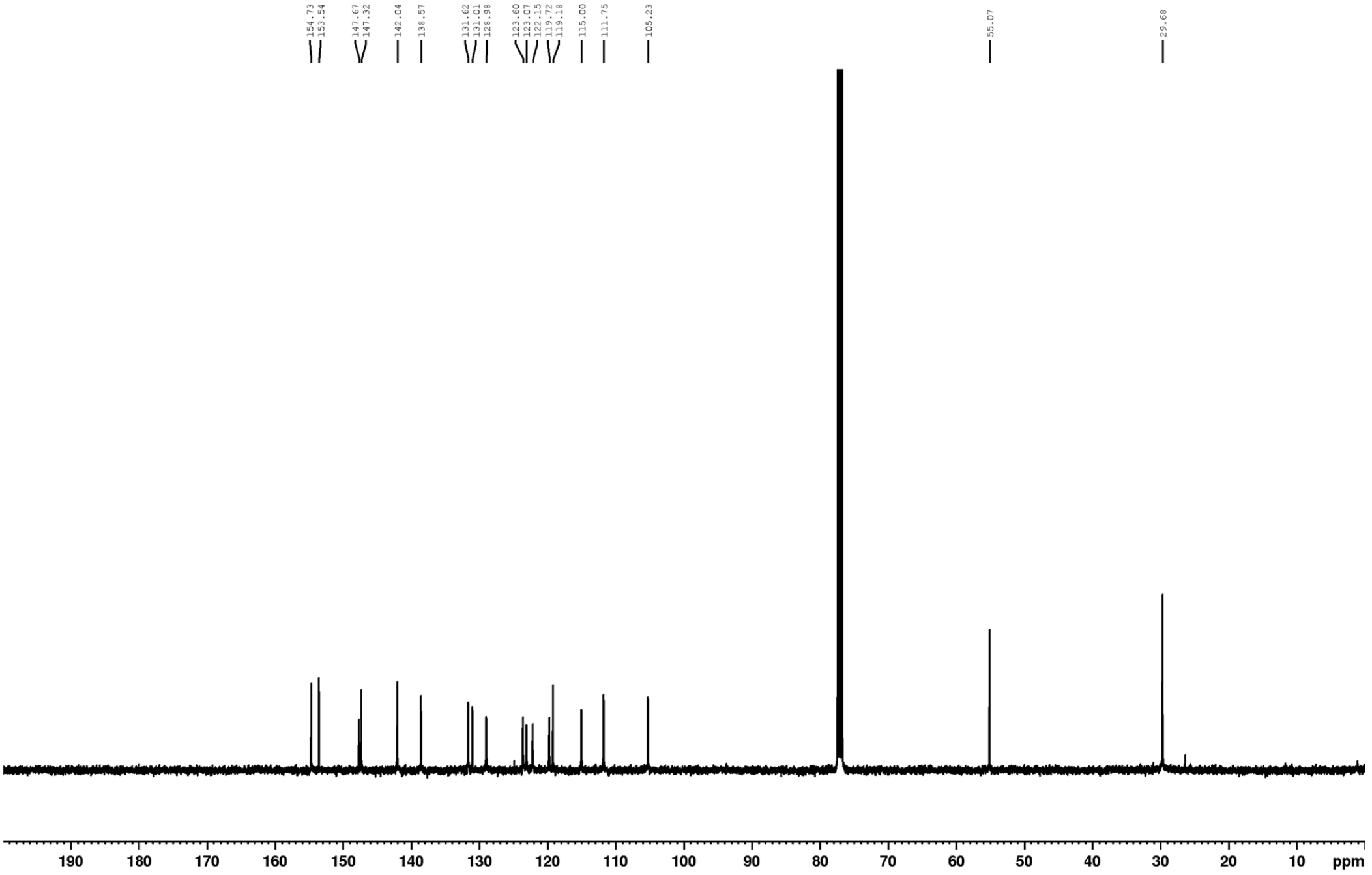
1-(4-chloro-3-nitrophenyl)-3-(2-(3-(thiophen-2-yl)phenyl)propan-2-yl)urea (35)



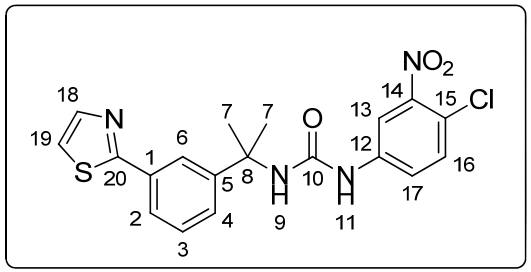

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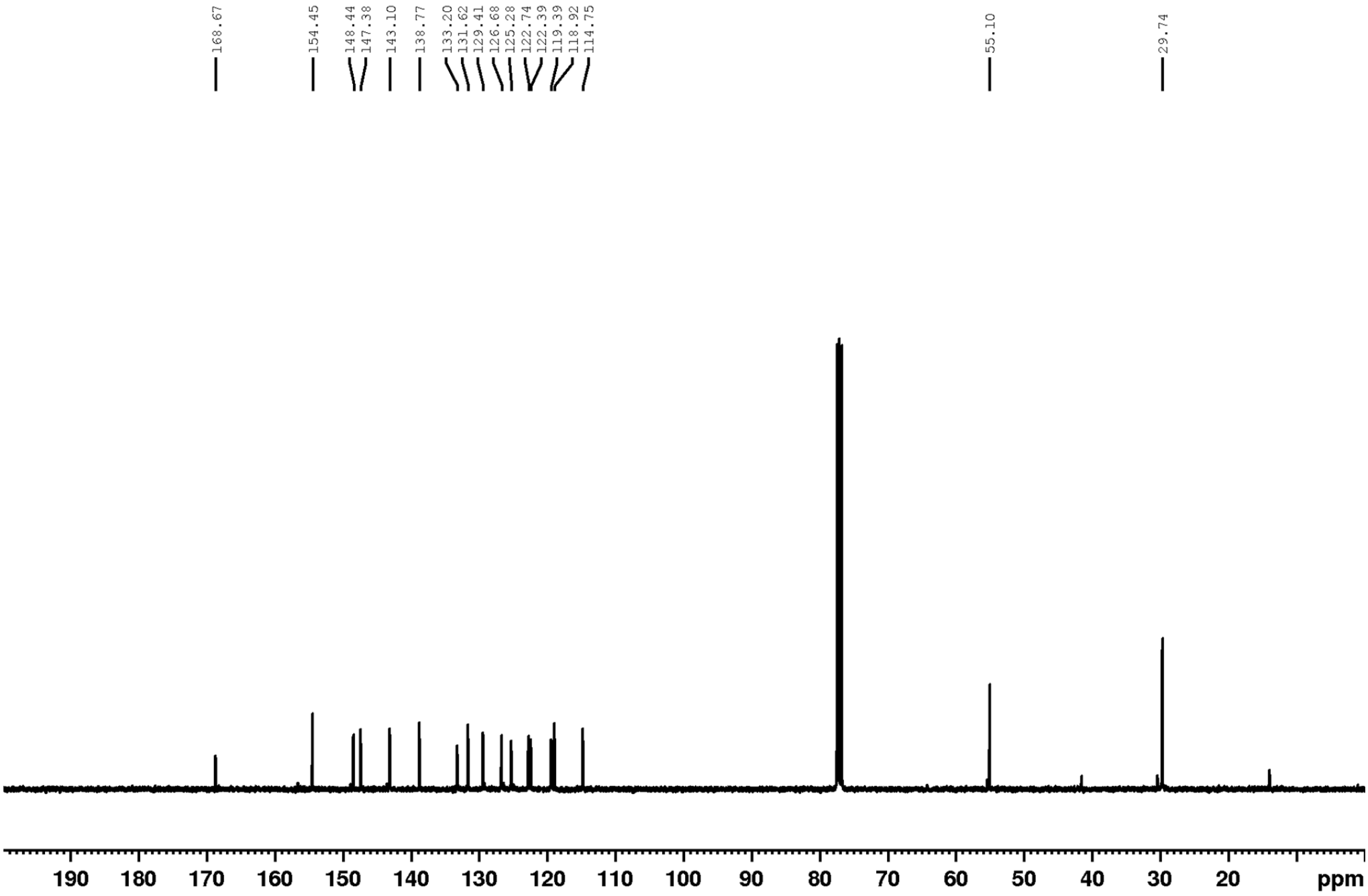
1-(4-chloro-3-nitrophenyl)-3-(2-(3-(furan-2-yl)phenyl)propan-2-yl)urea (36)



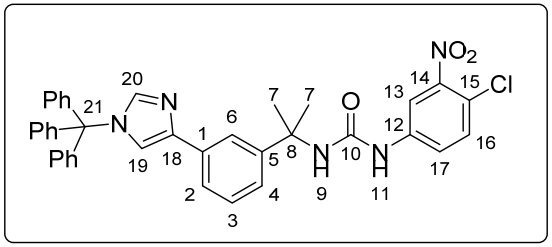

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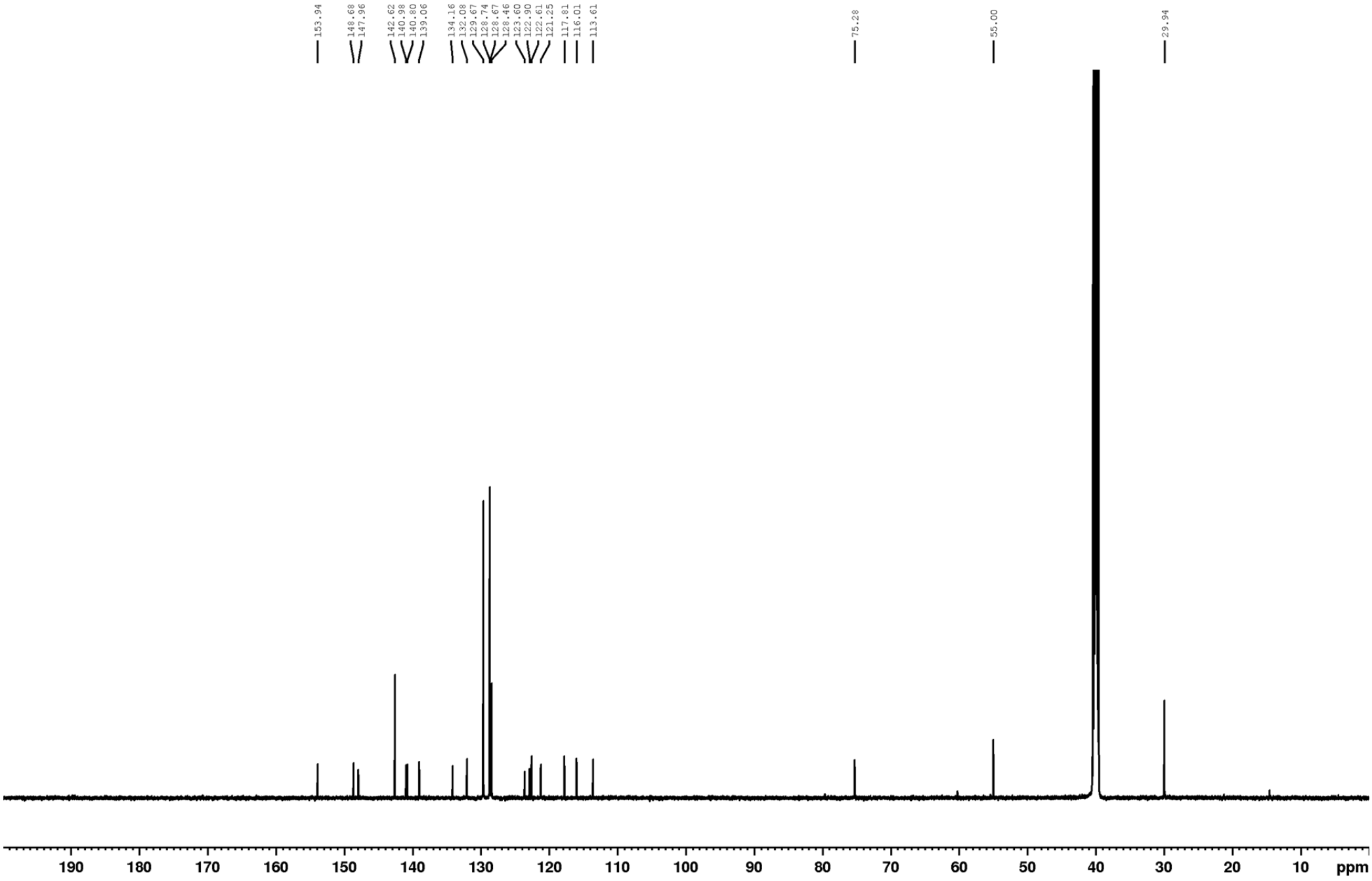
1-(4-chloro-3-nitrophenyl)-3-(2-(3-(thiazol-2-yl)phenyl)propan-2-yl)urea (37)



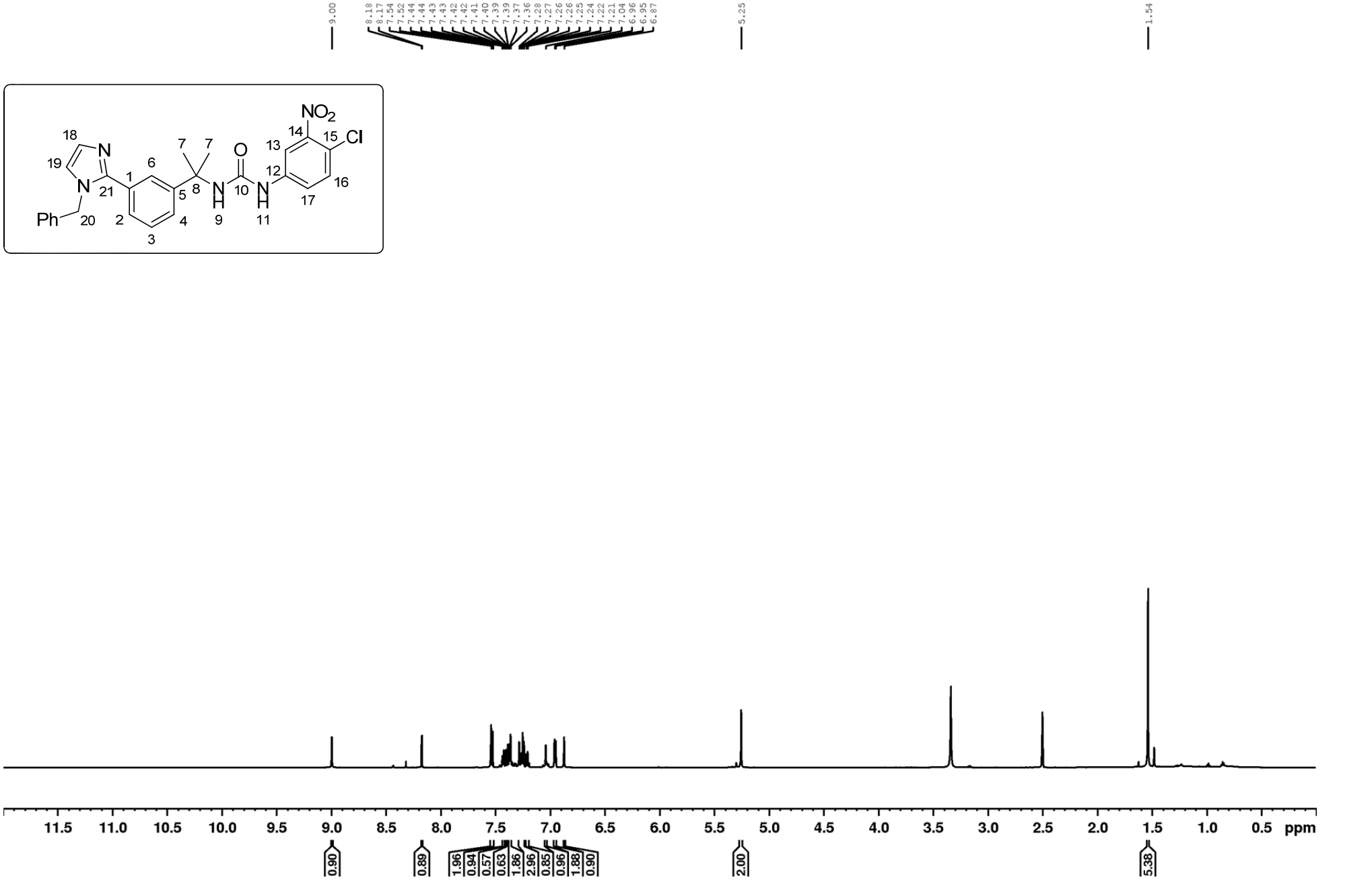

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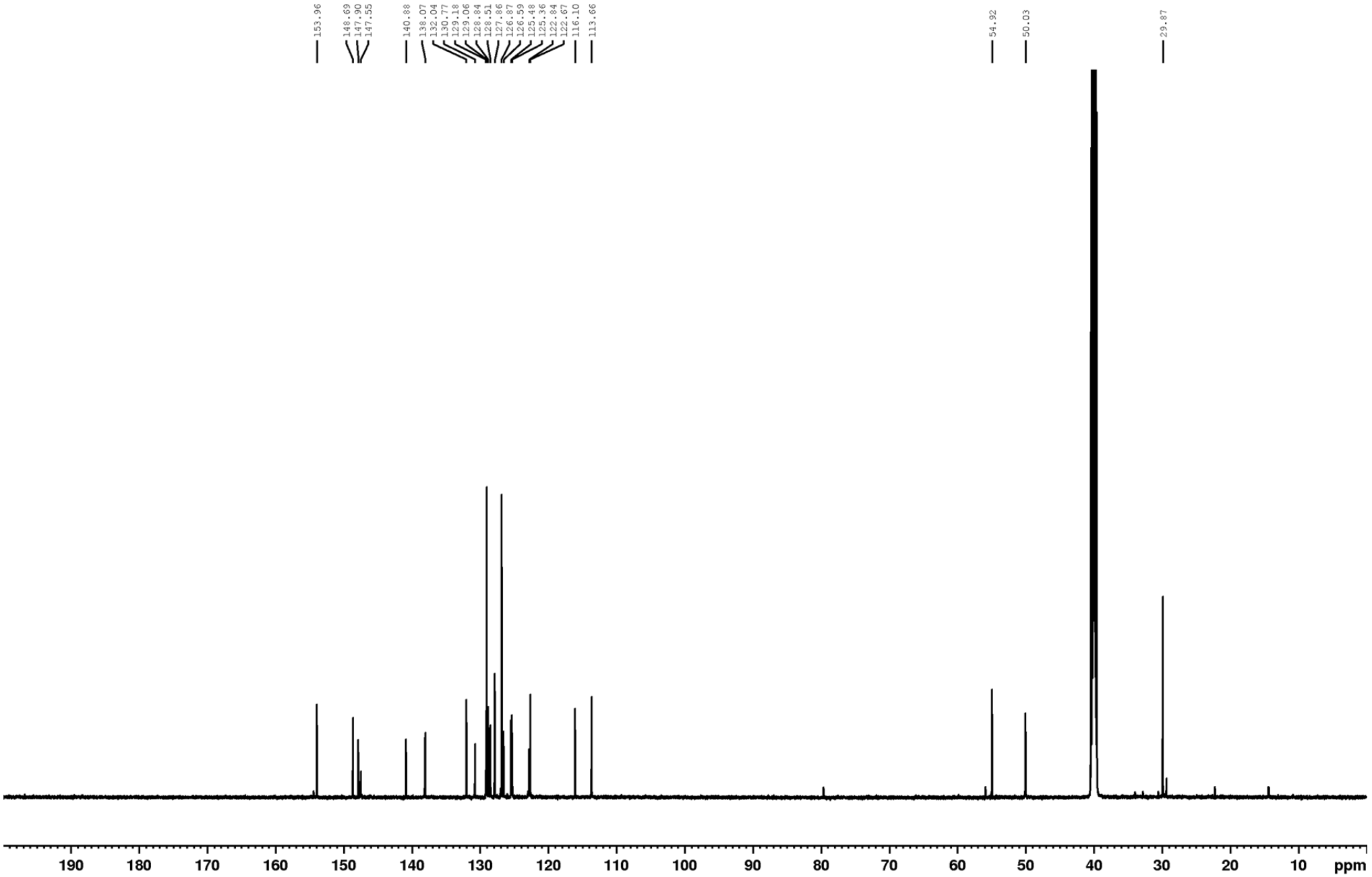
1-(4-chloro-3-nitrophenyl)-3-(2-(3-(1-trityl-1*H*-imidazol-4-yl)phenyl)propan-2-yl)urea (38)



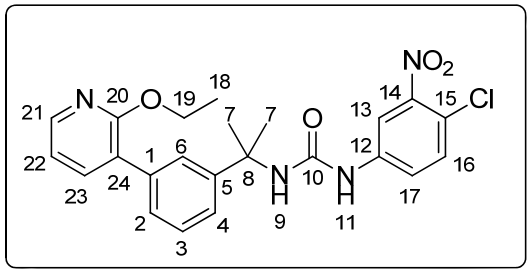

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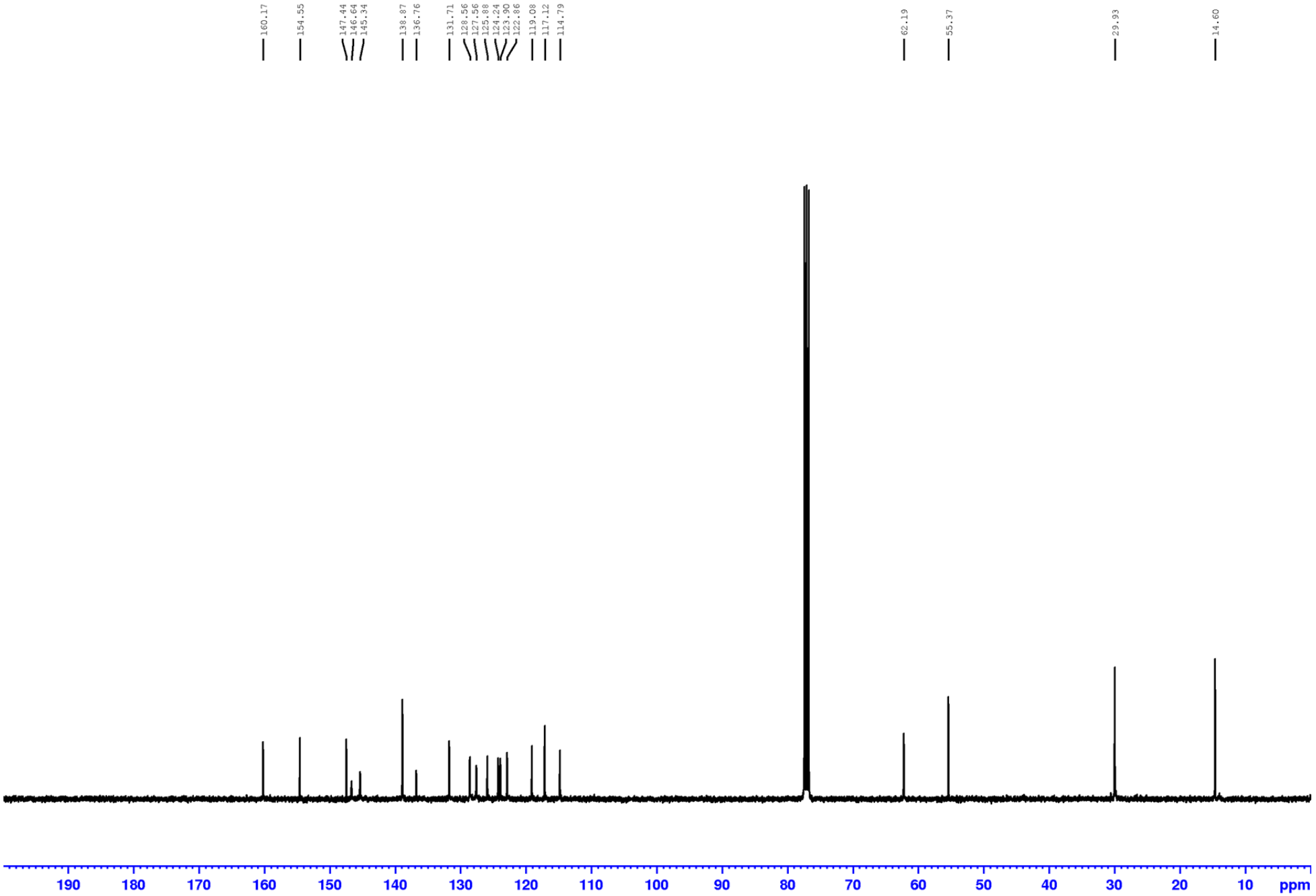
1-(2-(3-(1-benzyl-1*H*-imidazol-2-yl)phenyl)propan-2-yl)-3-(4-chloro-3-nitrophenyl)urea (39)



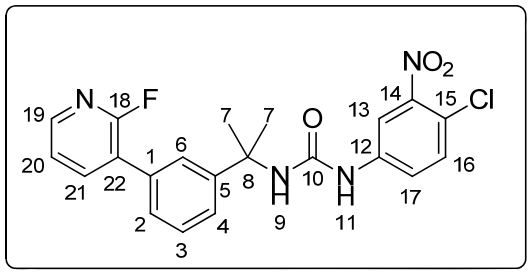

153.96
148.69
147.90
147.55
140.88
138.07
132.04
130.77
129.18
129.06
128.84
128.51
127.86
126.87
126.59
125.48
125.36
122.84
122.67
116.10
113.66
54.92
50.03
29.87
190
180
170
160
150
140
130
120
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90
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30
20
10
ppm

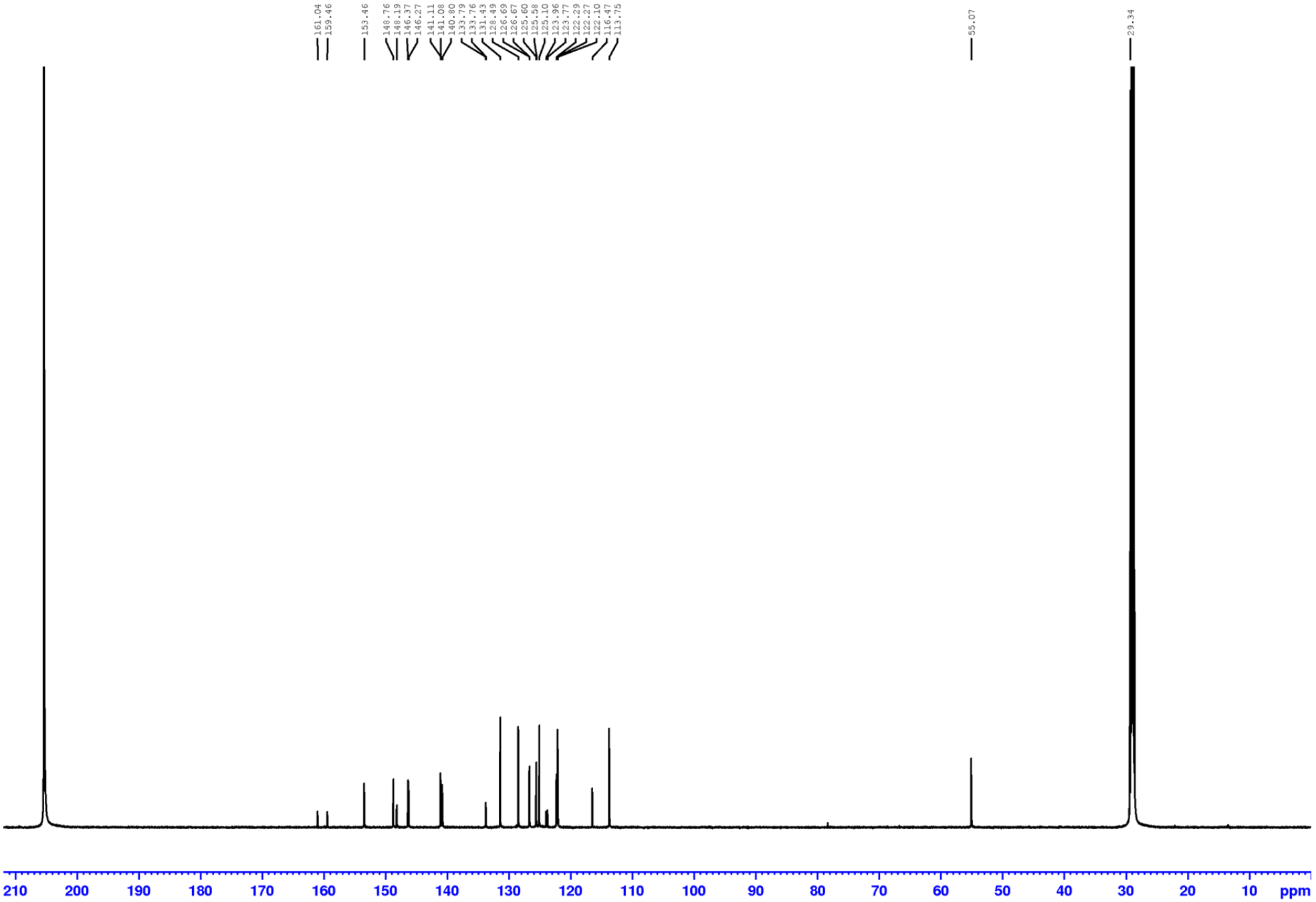
1-(4-chloro-3-nitrophenyl)-3-(2-(3-(2-ethoxypyridin-3-yl)phenyl)propan-2-yl)urea (40)



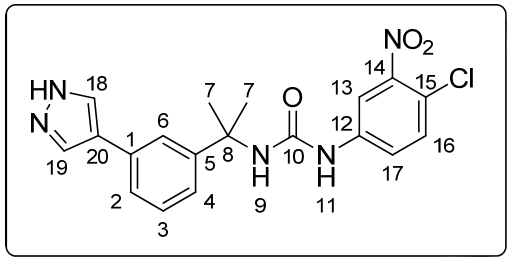

160.17
154.55
147.44
146.64
145.34
138.87
136.76
131.71
128.56
127.56
125.88
124.24
123.90
122.86
119.08
117.12
114.79
62.19
55.37
29.93
14.60
190
180
170
160
150
140
130
120
110
100
90
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70
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30
20
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ppm

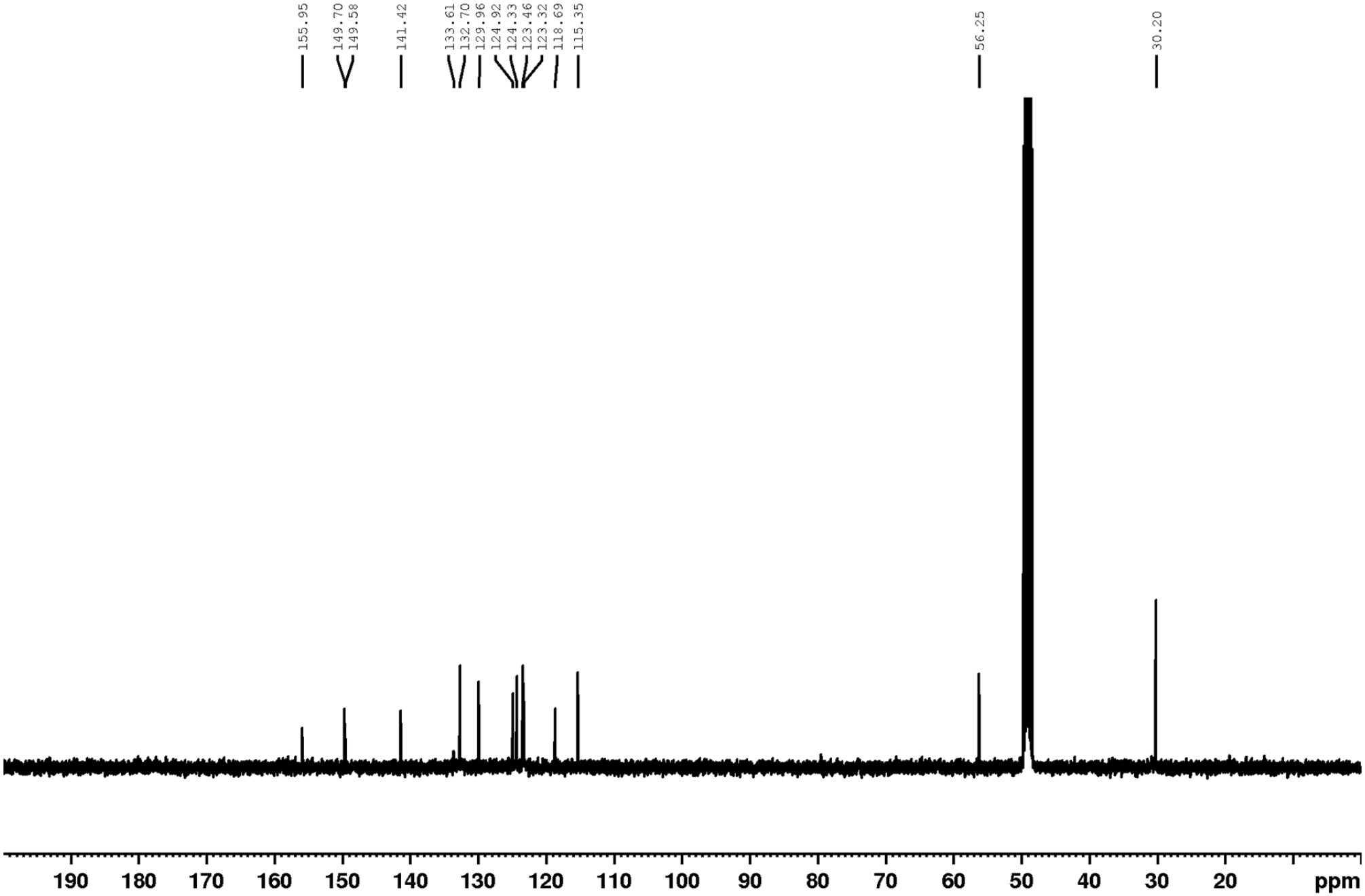
1-(4-chloro-3-nitrophenyl)-3-(2-(3-(2-fluoropyridin-3-yl)phenyl)propan-2-yl)urea (41)



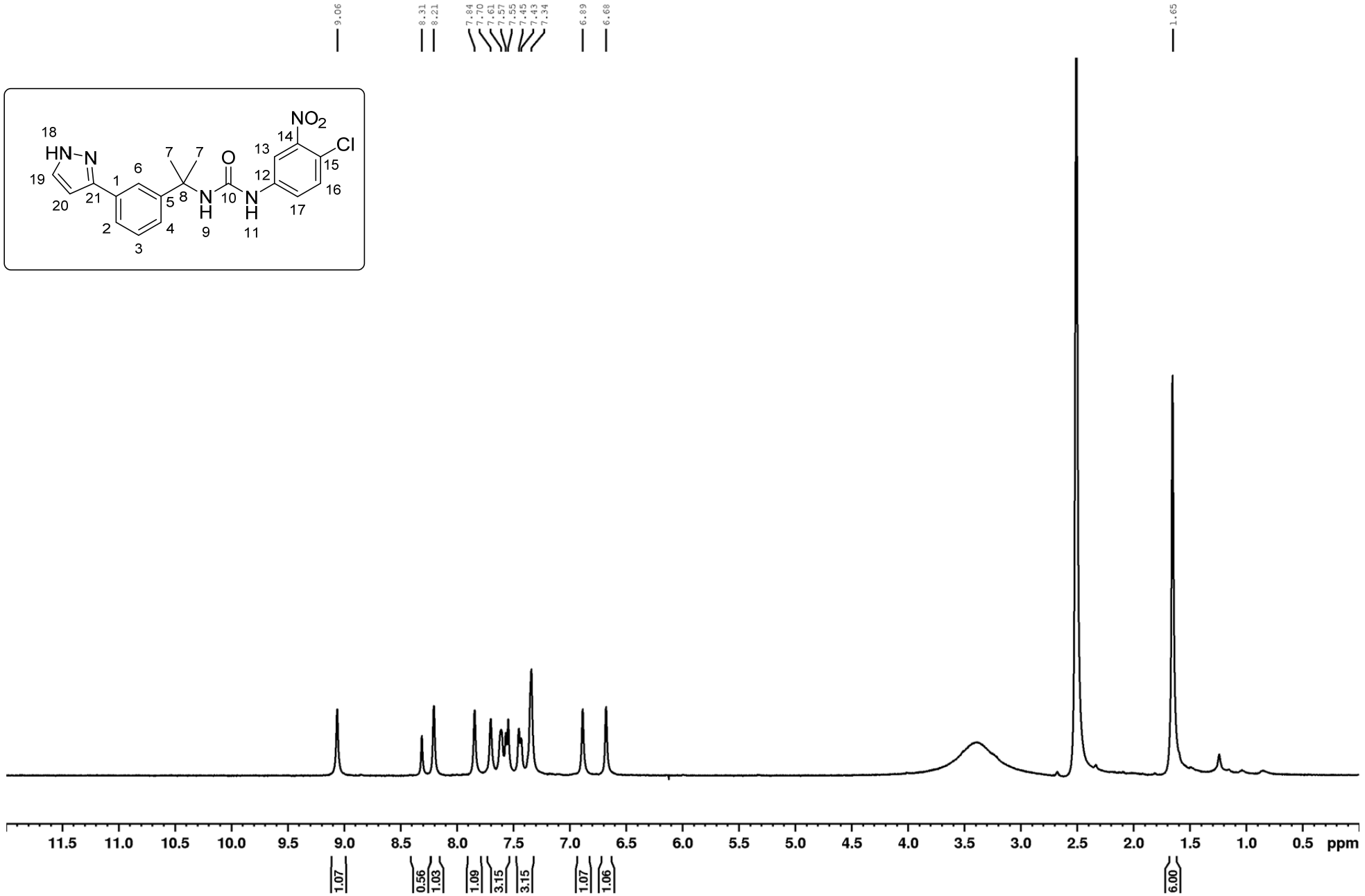

161.04
159.46
153.46
148.76
148.19
146.37
146.27
141.11
141.08
140.80
133.79
133.76
131.43
128.49
126.69
126.67
125.60
125.58
125.10
123.96
123.77
122.29
122.27
122.10
116.47
113.75
55.07
29.34
210
200
190
180
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140
130
120
110
100
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80
70
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50
40
30
20
10
ppm

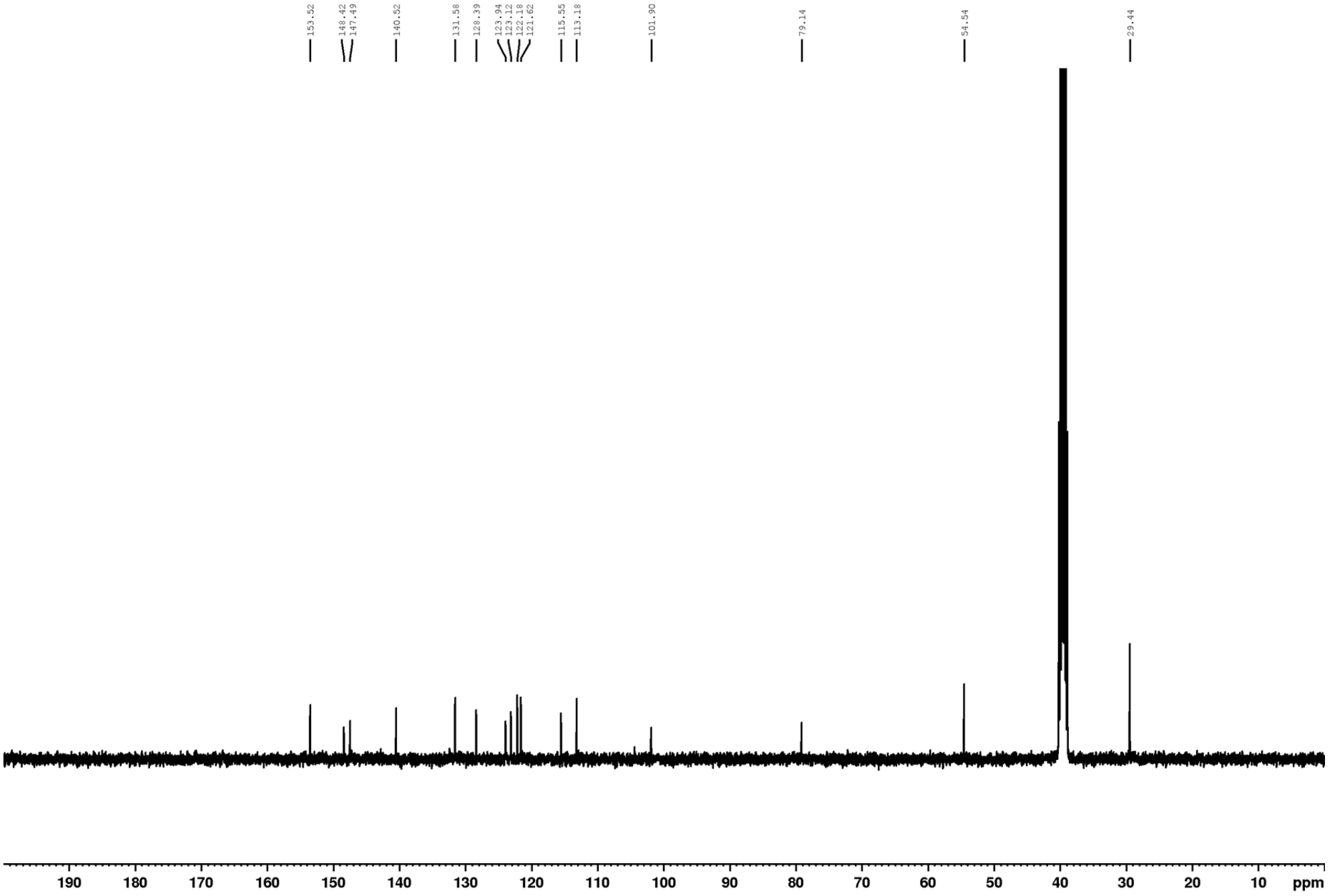
1-(2-(3-(1*H*-pyrazol-4-yl)phenyl)propan-2-yl)-3-(4-chloro-3-nitrophenyl)urea (42)



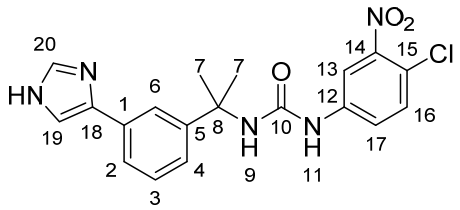

155.95
149.70
149.58
141.42
133.61
132.70
129.96
124.92
124.33
123.46
123.32
118.69
115.35
56.25
30.20
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

1-(2-(3-(1*H*-pyrazol-3-yl)phenyl)propan-2-yl)-3-(4-chloro-3-nitrophenyl)urea (43)

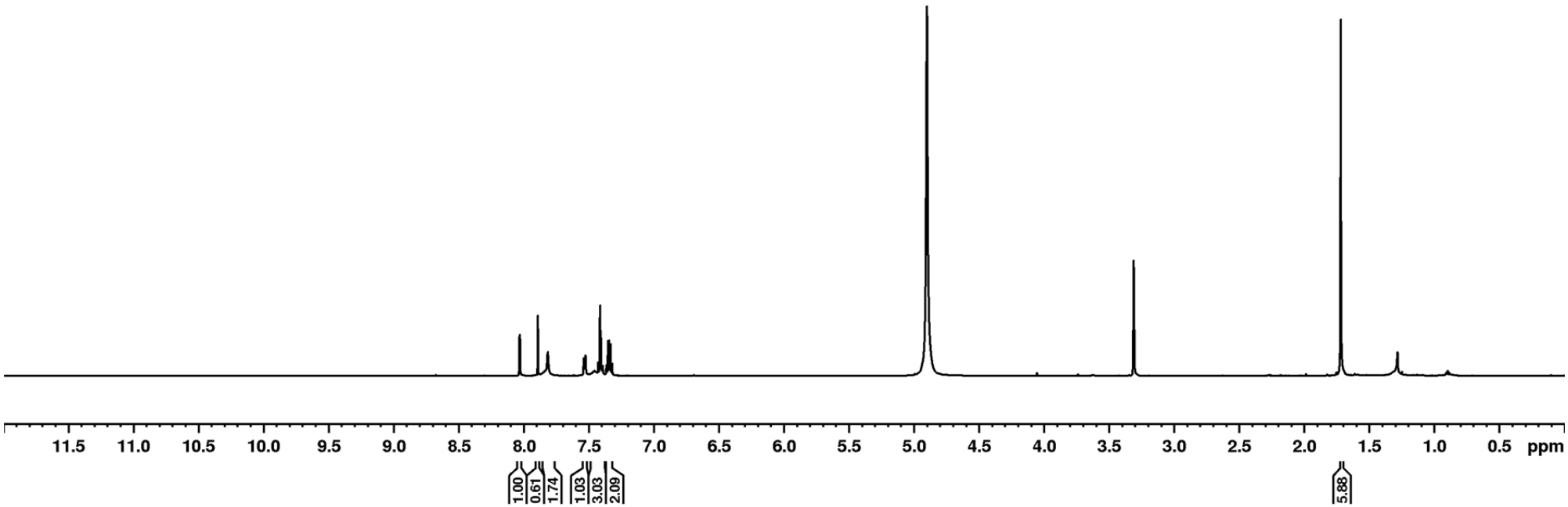


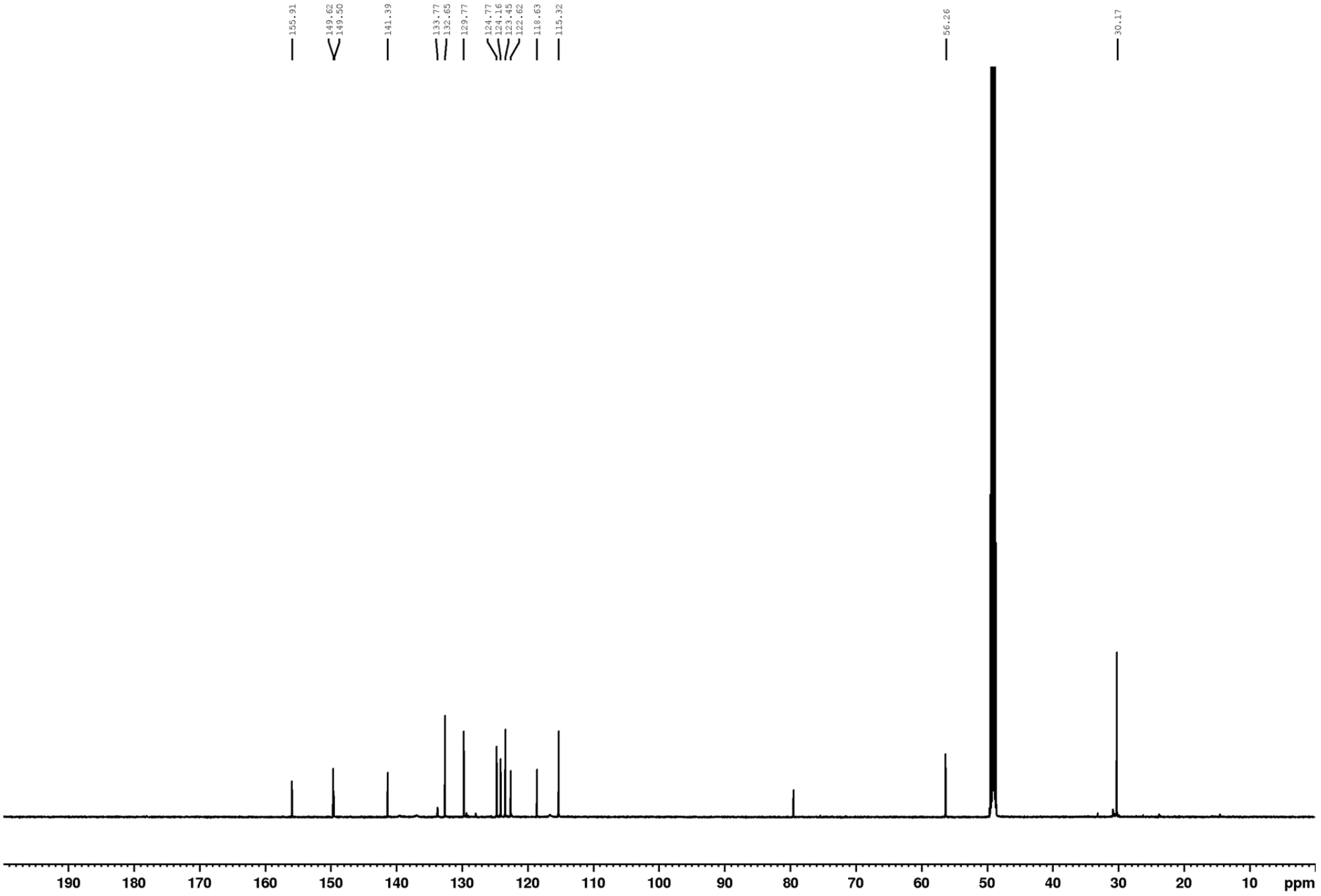

153.52
148.42
147.49
140.52
131.58
128.39
123.94
123.12
122.18
121.62
115.55
113.18
101.90
79.14
54.54
29.44
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

1-(2-(3-(1*H*-imidazol-4-yl)phenyl)propan-2-yl)-3-(4-chloro-3-nitrophenyl)urea (44)








155.91
149.62
149.50
141.39
133.77
132.65
129.77
124.77
124.16
123.45
122.62
118.63
115.32
56.26
30.17
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

Determination of compound stability using mouse liver microsomes: Each of **42**-**44** (5 μM) was incubated with mouse liver microsomes at 37 °C. The solution contained microsomal protein in 100 mM potassium phosphate, 2 mM NADPH, 3 mM $MgCl_2$ at pH 7.4. A control was run for each test agent omitting NADPH to detect NADPH-free degradation. Aliquots were removed at various time points and mixed with an equal volume of ice-cold Stop Solution (0.3% acetic acid in MeCN containing diclofenac). Stopped reactions were incubated for at least ten minutes at -20 °C, and an additional volume of water was added. The samples were centrifuged to remove precipitated protein, and the supernatants were analysed by LC/MS.