Selectivity of *N*- versus *O*-Alkylation in Mitsunobu Reactions with Various Quinolinols and Isoquinolinols

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Supporting Information

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1. General Information

1.1. Reagents

The majority of reagents were published from Aldrich when available. The same bottles of PPh_3, DEAD (40% by weight in toluene) and THF were used for every experiment in the publication as to keep all reaction conditions near identical.

1.2. Chromatography

Purification was carried out on a Waters preparatory system using reverse-phase chromatography unless otherwise noted. The method used eluents A (water with 0.1% trifluoroacetic acid) and B (acetonitrile). The method started at 25% B for 0 – 1 min, then a linear gradient of 25% - 85% B for 1 – 8 min, followed by a wash with 100% B for 1 min. The fractions containing the desired product (as determined by analytical HPLC-MS) were combined, frozen at -78 °C, and lyophilized to yield the final product.

1.3. Nuclear Magnetic Resonance Spectroscopy

Proton (^{1}H NMR) and carbon (^{13}C NMR) spectra were recorded on a Bruker Avance 600 MHz spectrometer. All pulse sequences were used as provided. All NMR spectra were Fourier transformed, manually phase corrected, and auto baseline corrected. 1H NMR spectra chemical shifts (δ) are reported in parts per million (ppm) and were referenced to DMSO-d6 (δ 2.50 ppm). Spectral data is reported as follows: chemical shift, multiplicity (s = singlet, br s = broad singlet; d = doublet, t = triplet, q = quartet, dd = doublet of doublets, dt = doublet of triplets, ddt = doublet of doublet of triplets, dtd= doublet of triplet of doublets, m = multiplet, br = broad), coupling constant (J) in Hertz (Hz), and integration. 13C NMR spectra chemical shifts (δ) are reported in parts per million (ppm) and were referenced to DMSO-d6 (δ 39.52 ppm). Some of the final compounds and isomers are not included in this publication as their purification from the reaction mixture's DEAD, triphenylphosphine oxide or corresponding isomer proved unsuccessful. Please contact the lead author if the crude ^{1}H or ^{13}C NMR from any of the unpublished compounds is wanted.

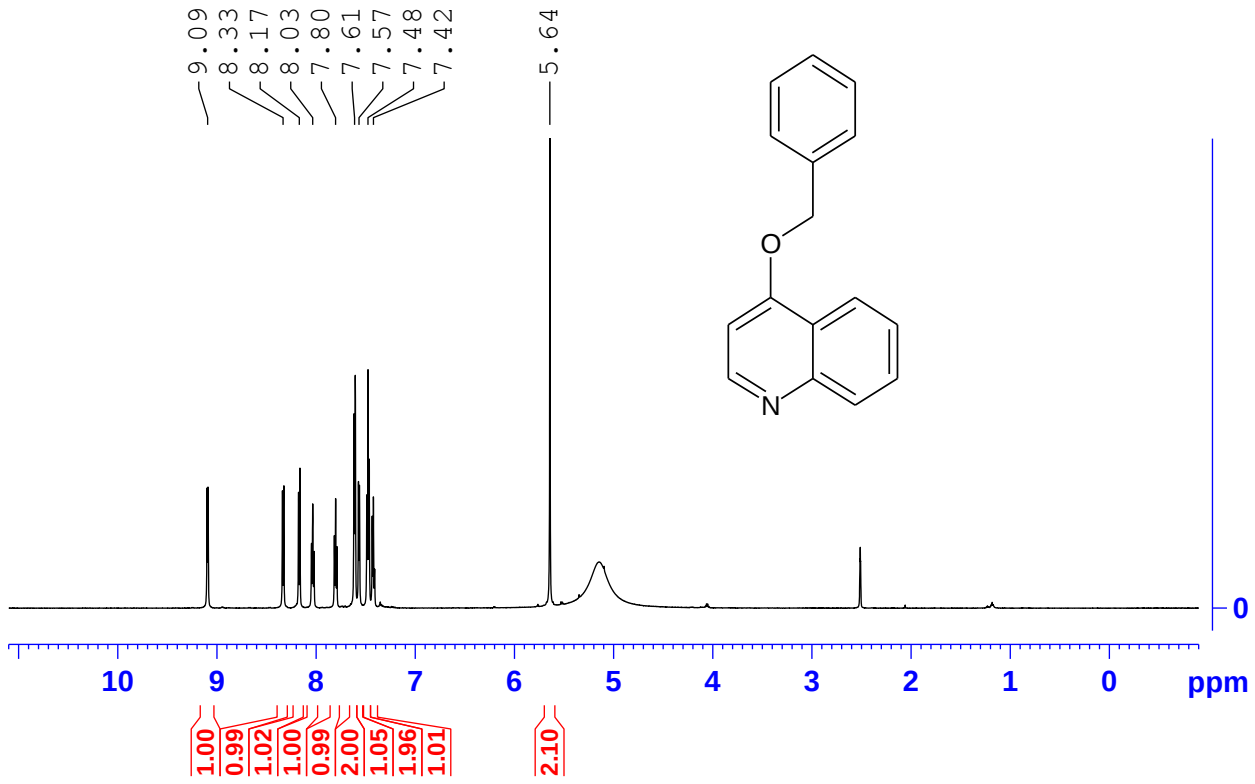
2. General Procedure

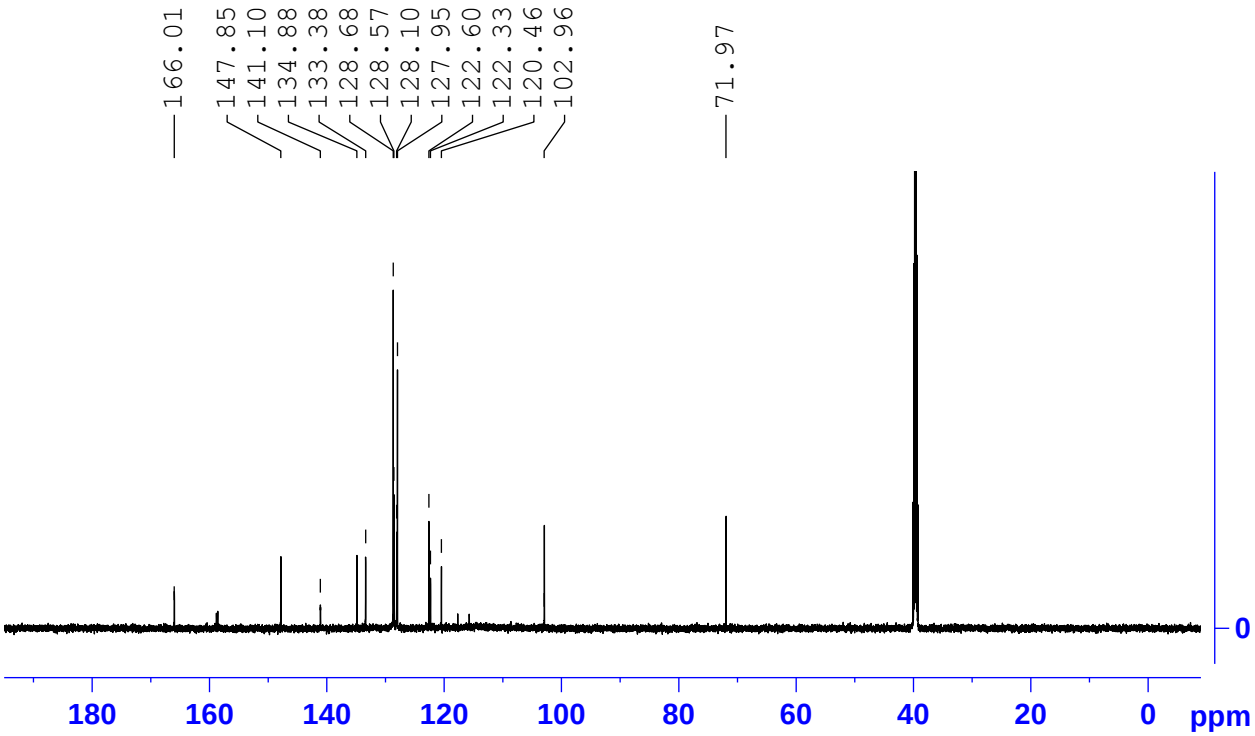
2.1. General Representative Procedure

Unless otherwise noted, this procedure below was adopted for each of the Mitsunobu reactions. PPh_3 (89 mg, 0.34 mmole, 2 eq) and the quinolinol or isoquinolinol (25 mg, 0.17 mmole, 1 eq) were combined in a glass vial and purged with nitrogen. THF (700 uL) was then added, followed by benzyl alcohol (44 uL, 0.34 mmole, 2 eq). A 40% by weight solution of DEAD in toluene (170 uL, 0.34 mmole, 1 eq) was then added drop-wise to keep the reaction temperature from rising. The reaction mixture was then shaken at room temperature overnight. The reaction mixture was then purified on a Waters preparative LC/MS system with a gradient of 0% to 60% ACN:H_2O over 7 minutes to give the desired product. The purified products were then characterized by ^{1}H and ^{13}C NMR. In most circumstances only the ^{1}H NMR and COSY were necessary for structure eludication. For reaction mixtures where the *N*- and *O*-alkylated products

were too close for separation, the ^{1}H NMR spectrum was used to determine the ratio of the two products.

Compound 1 Major





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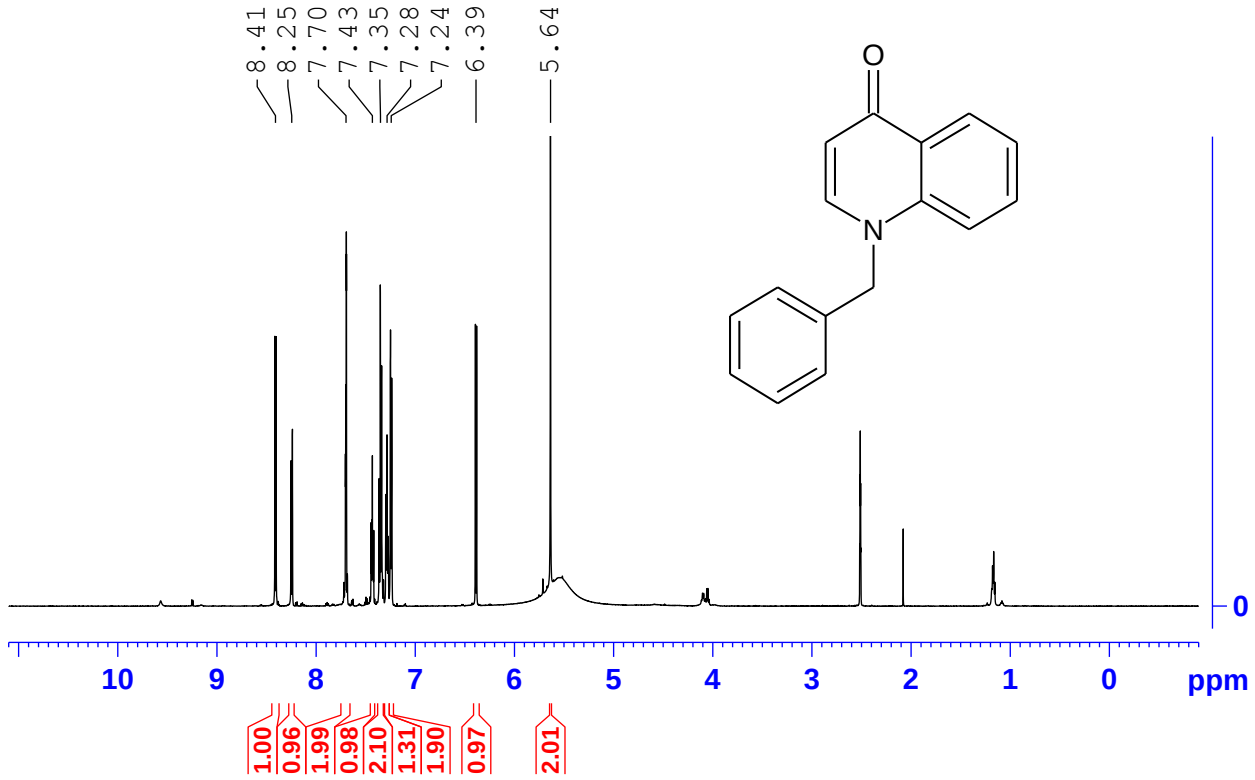

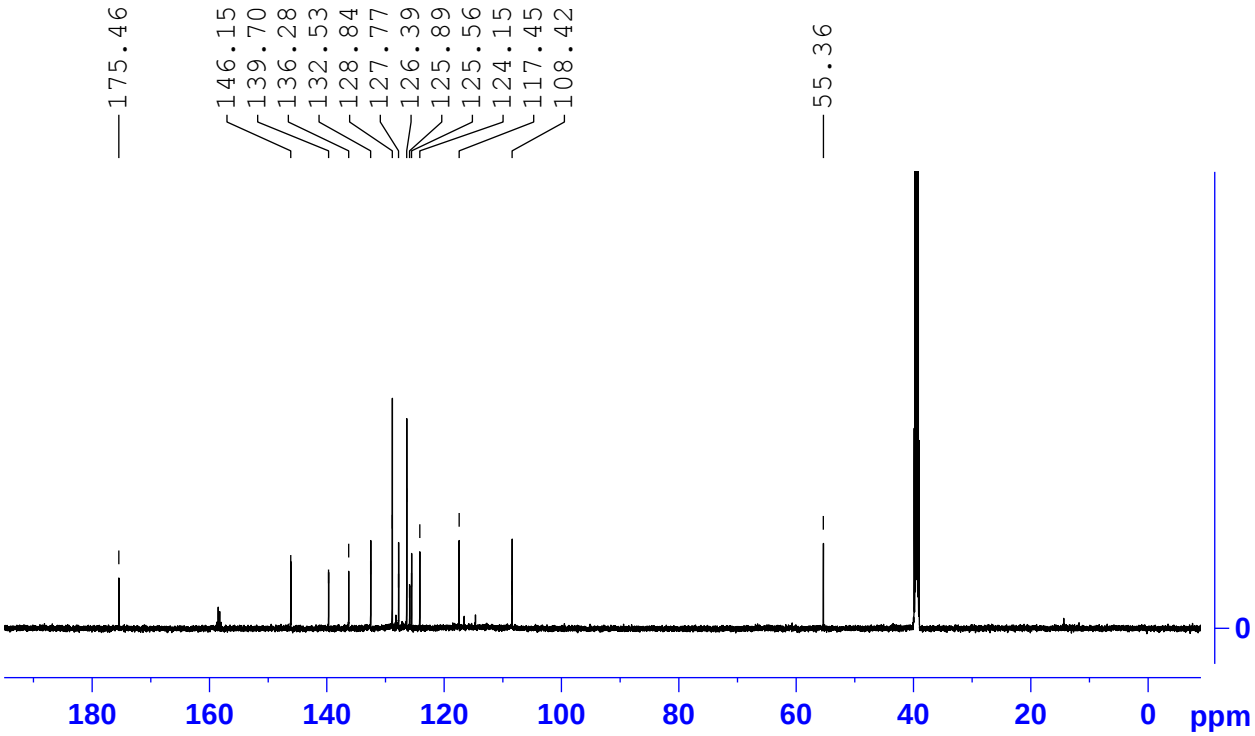

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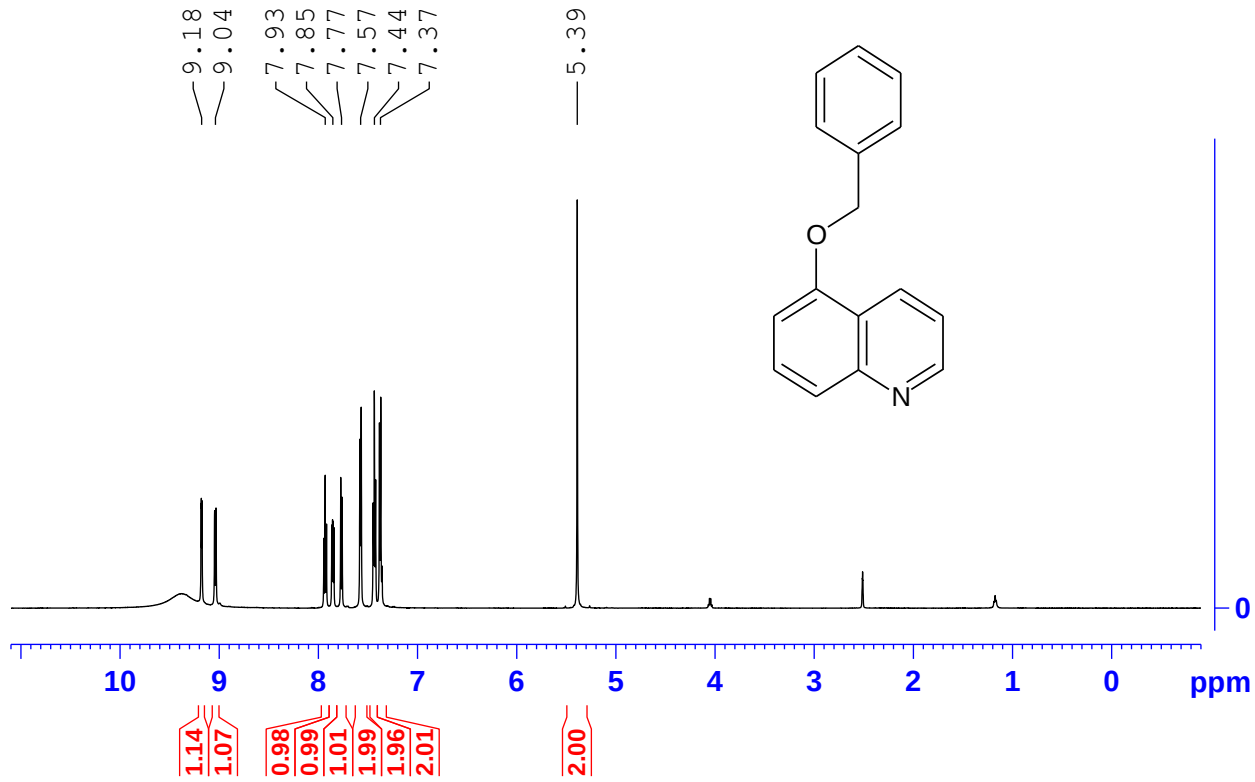

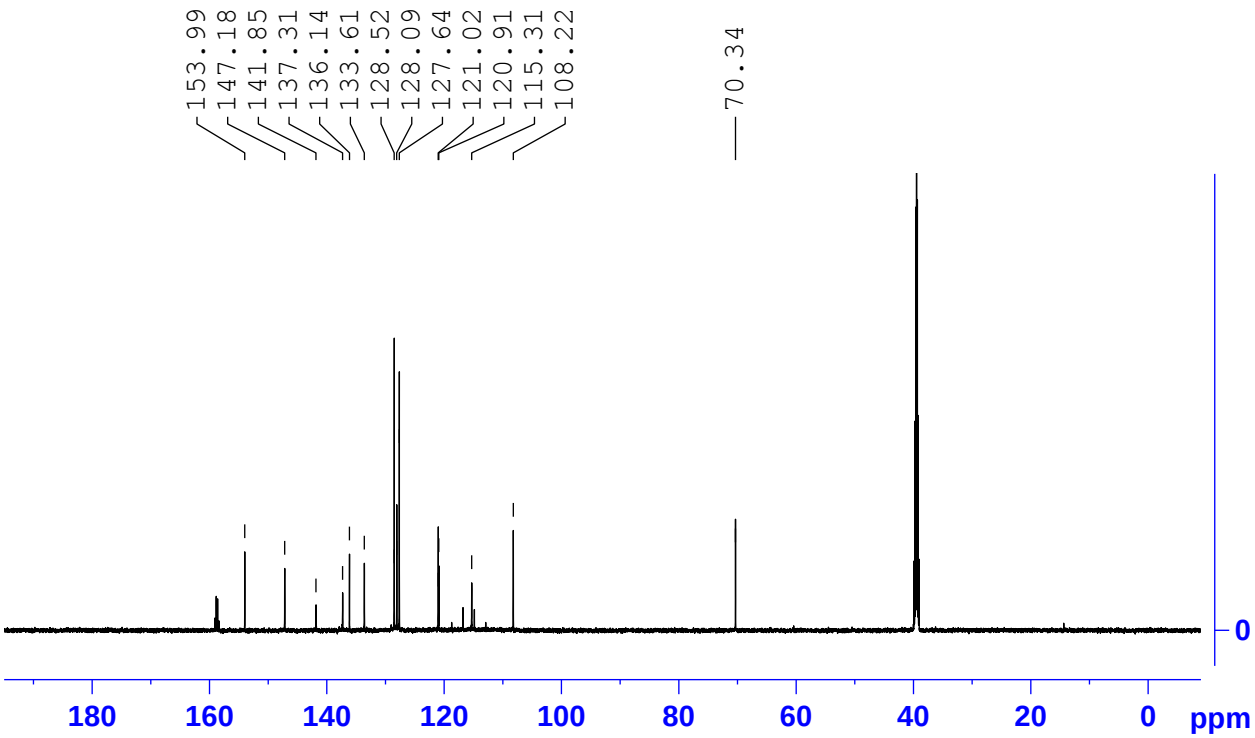

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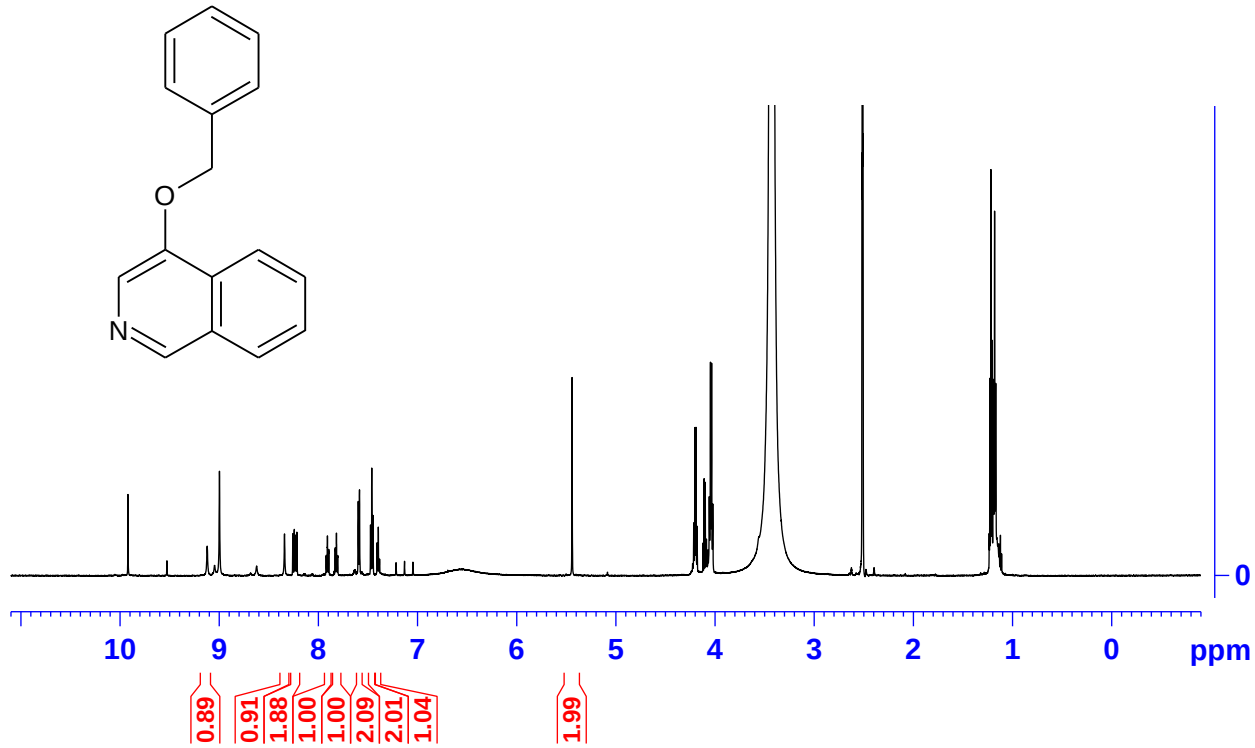
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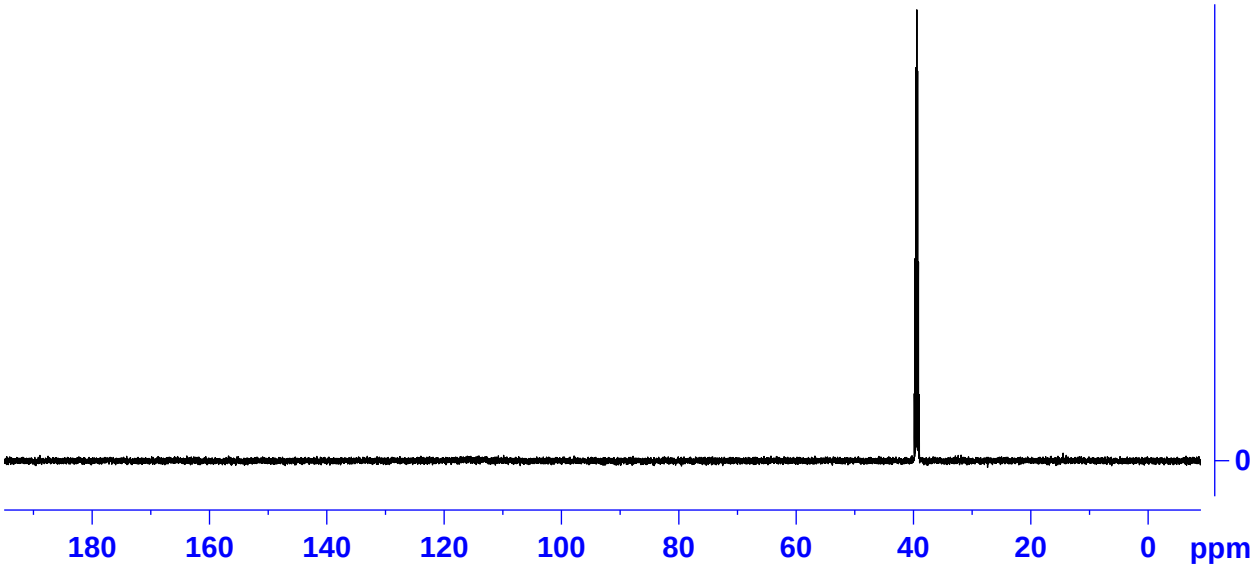
2.01
1.04
1.99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60
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0
ppm

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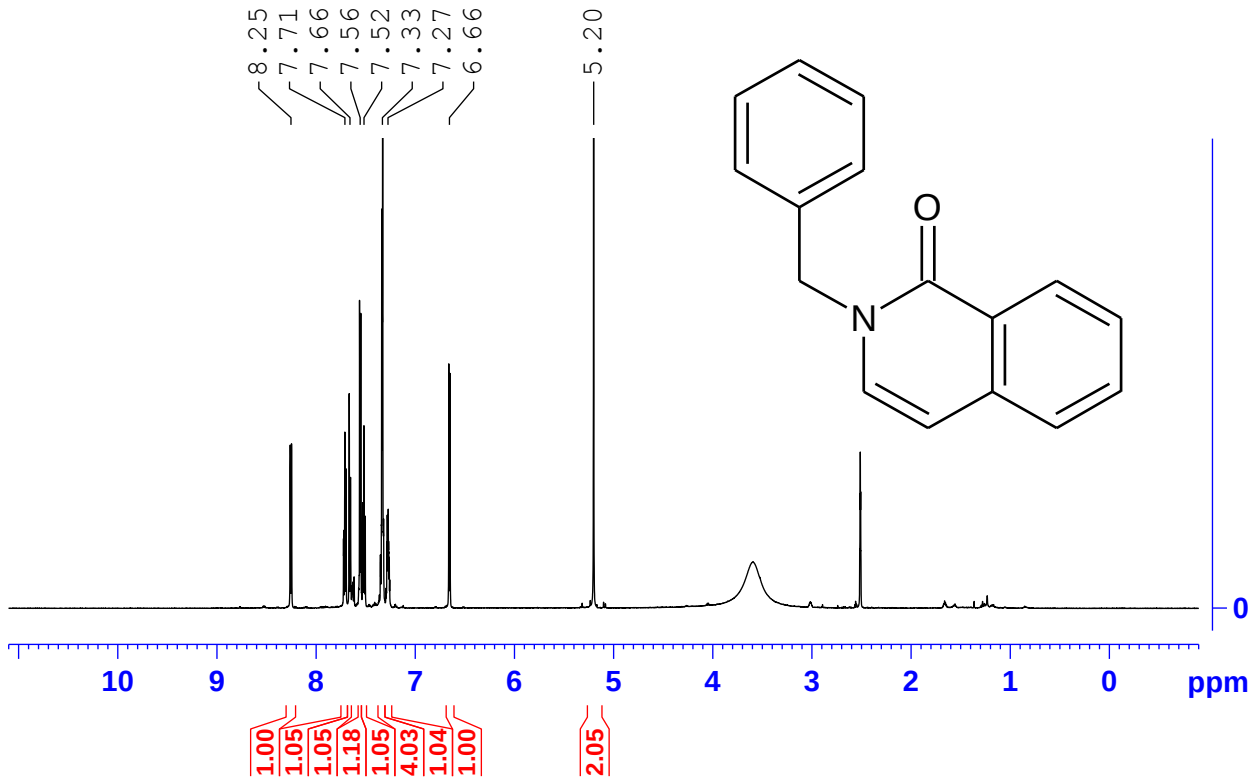

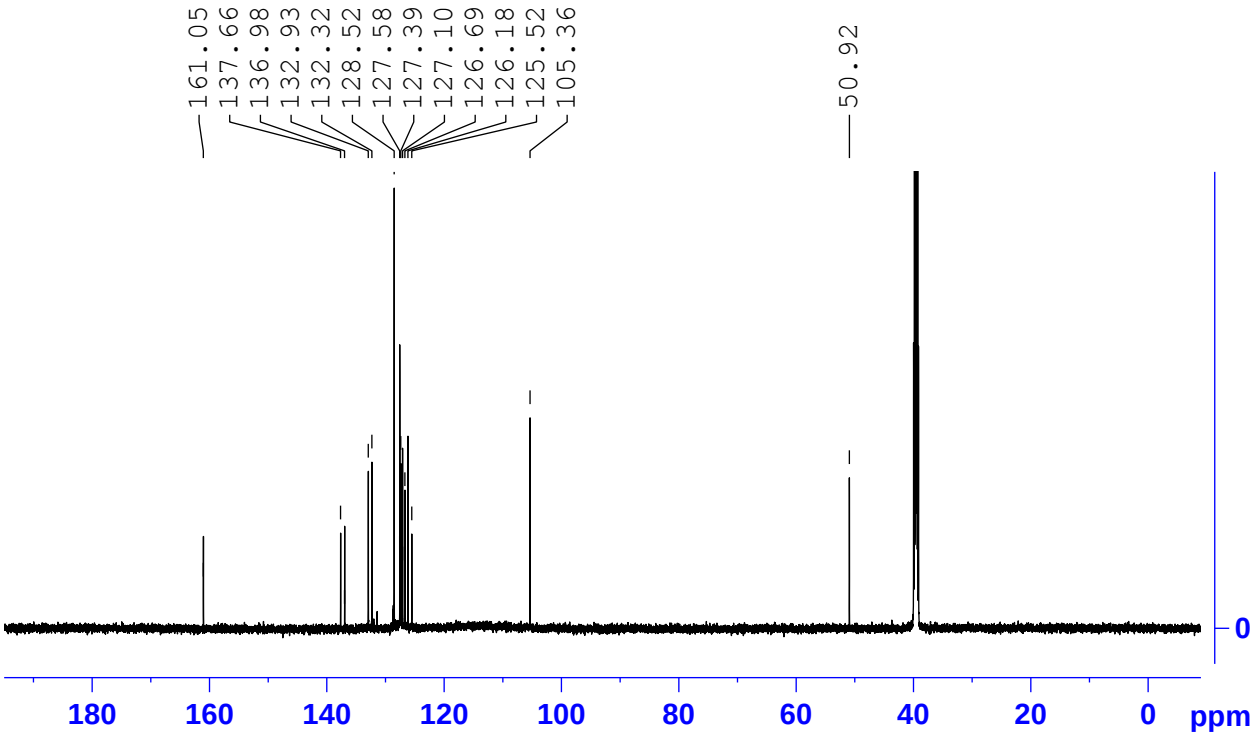

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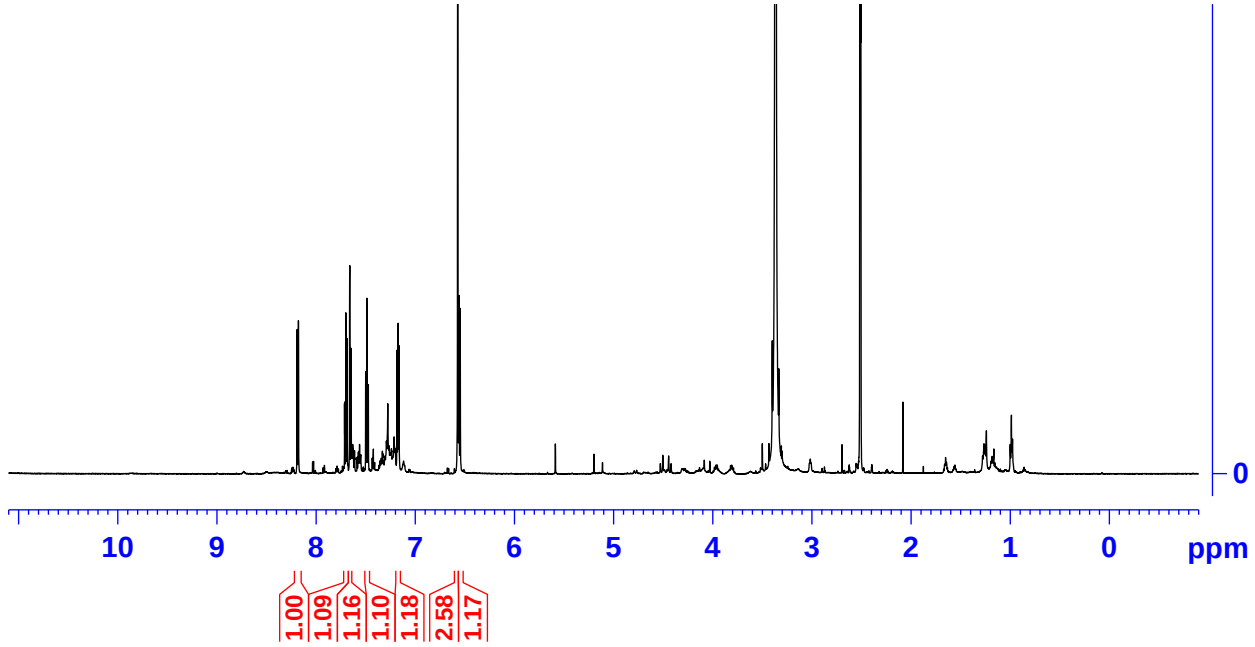

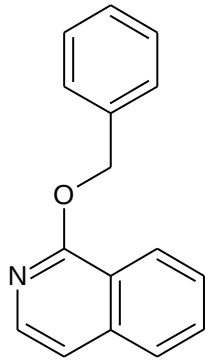

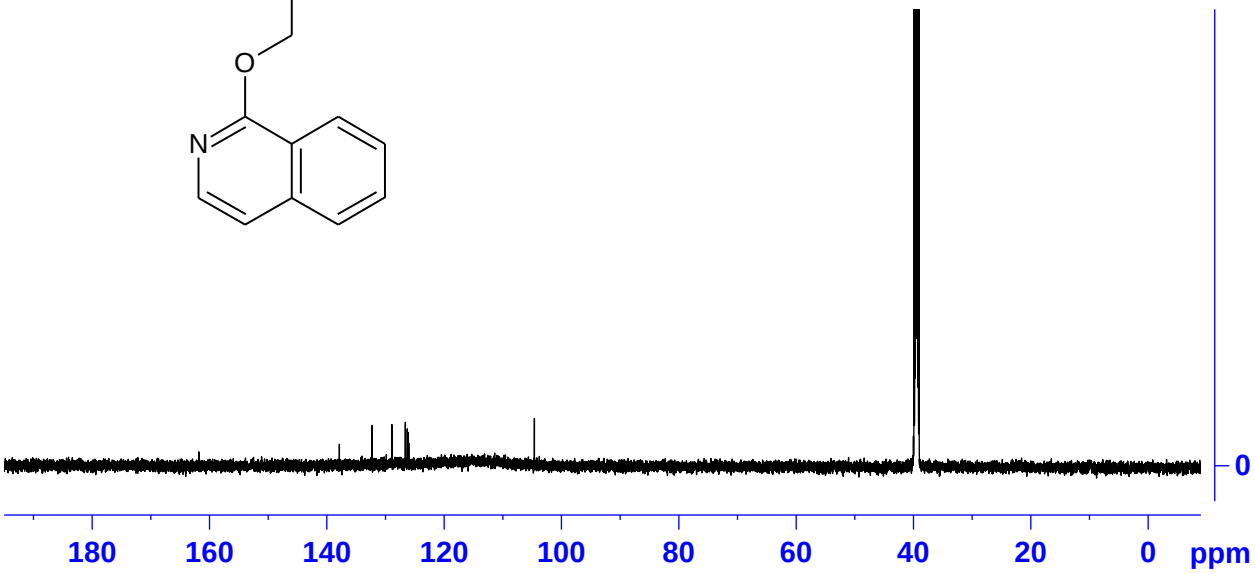

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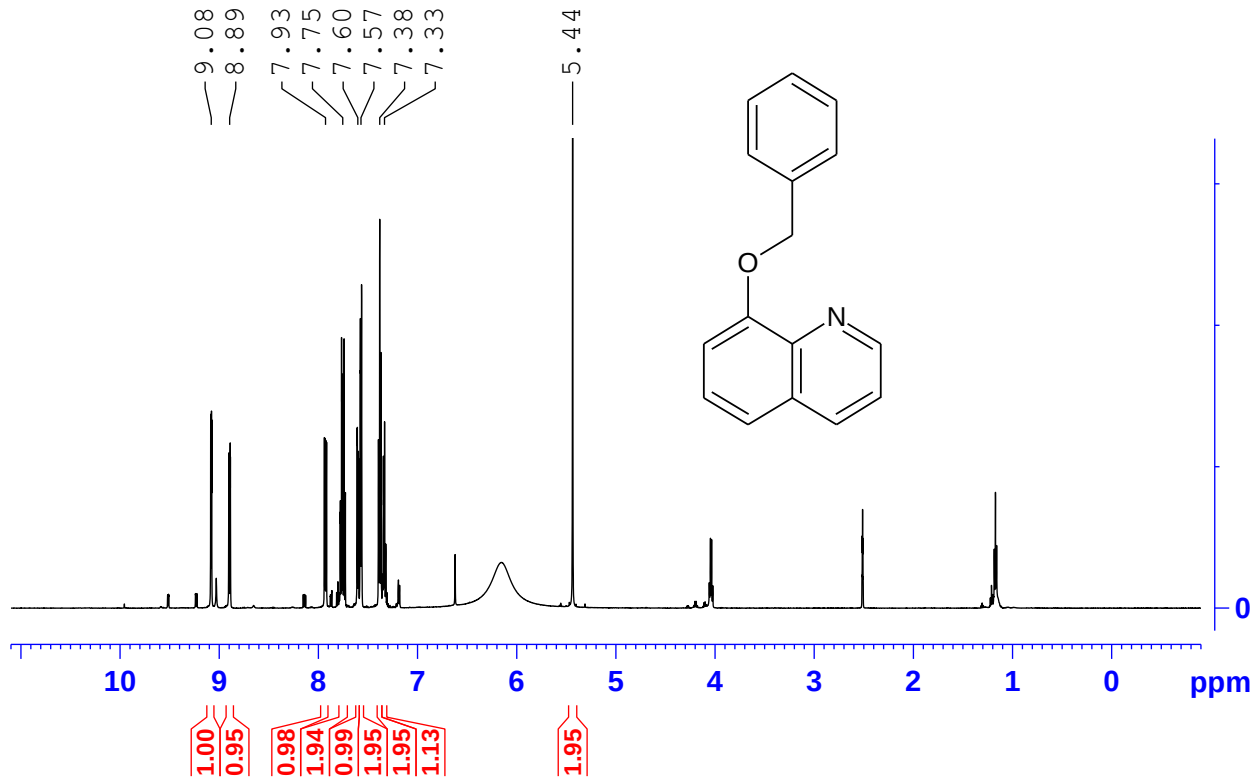
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6
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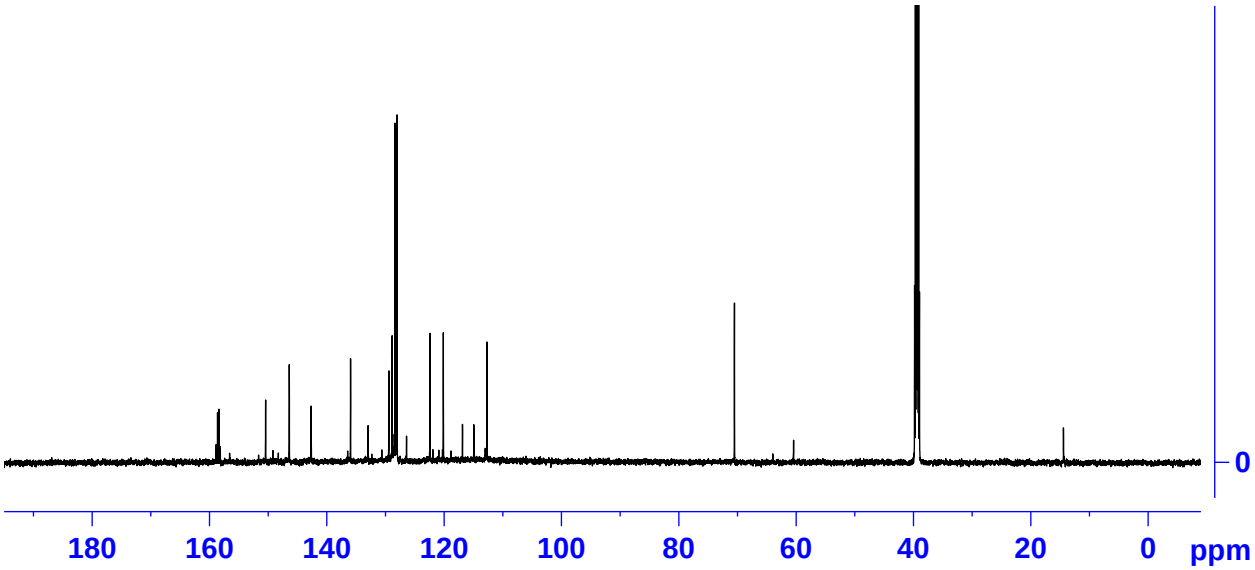
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0
ppm

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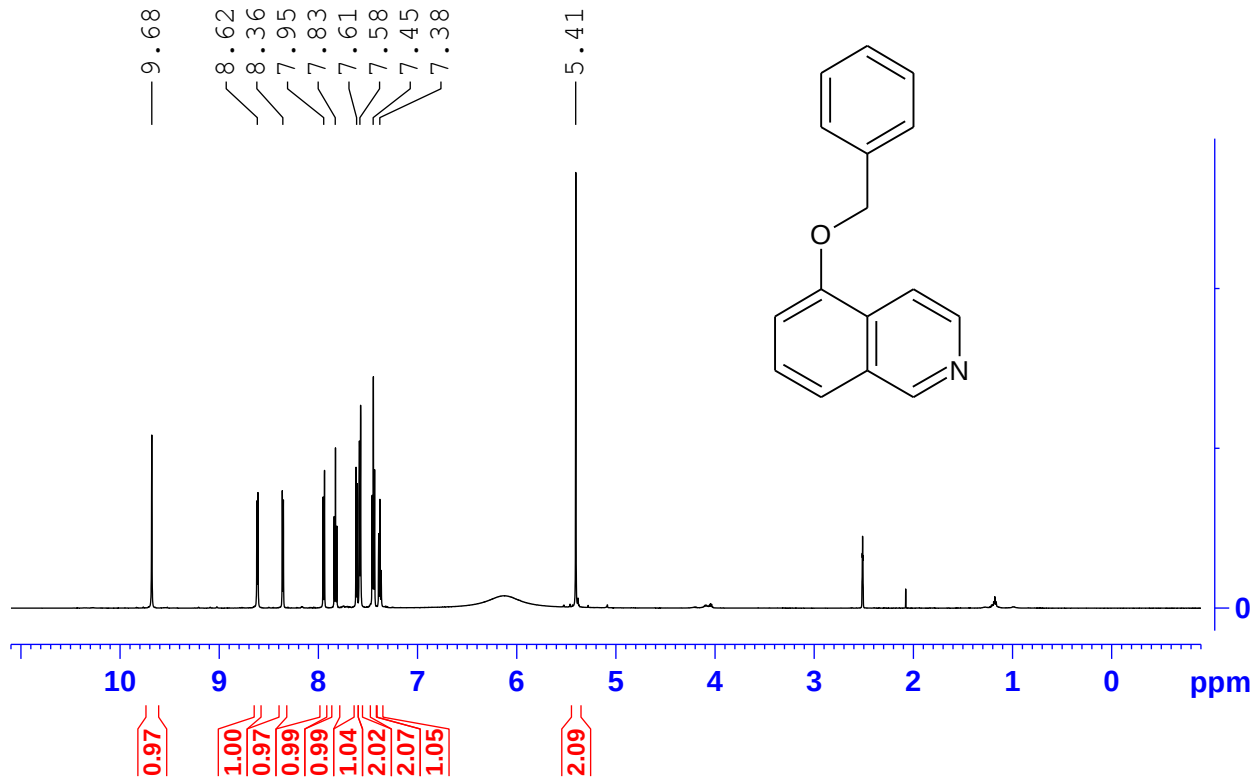
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8
7
6
5
4
3
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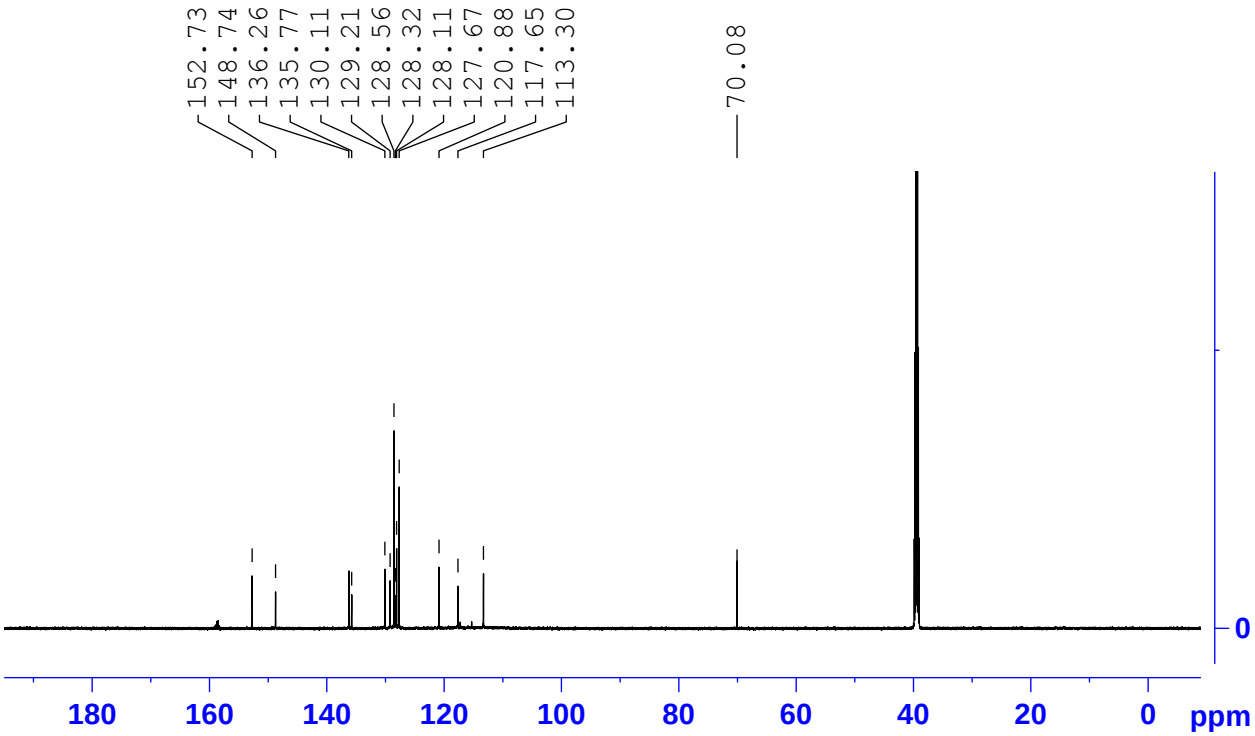
2.09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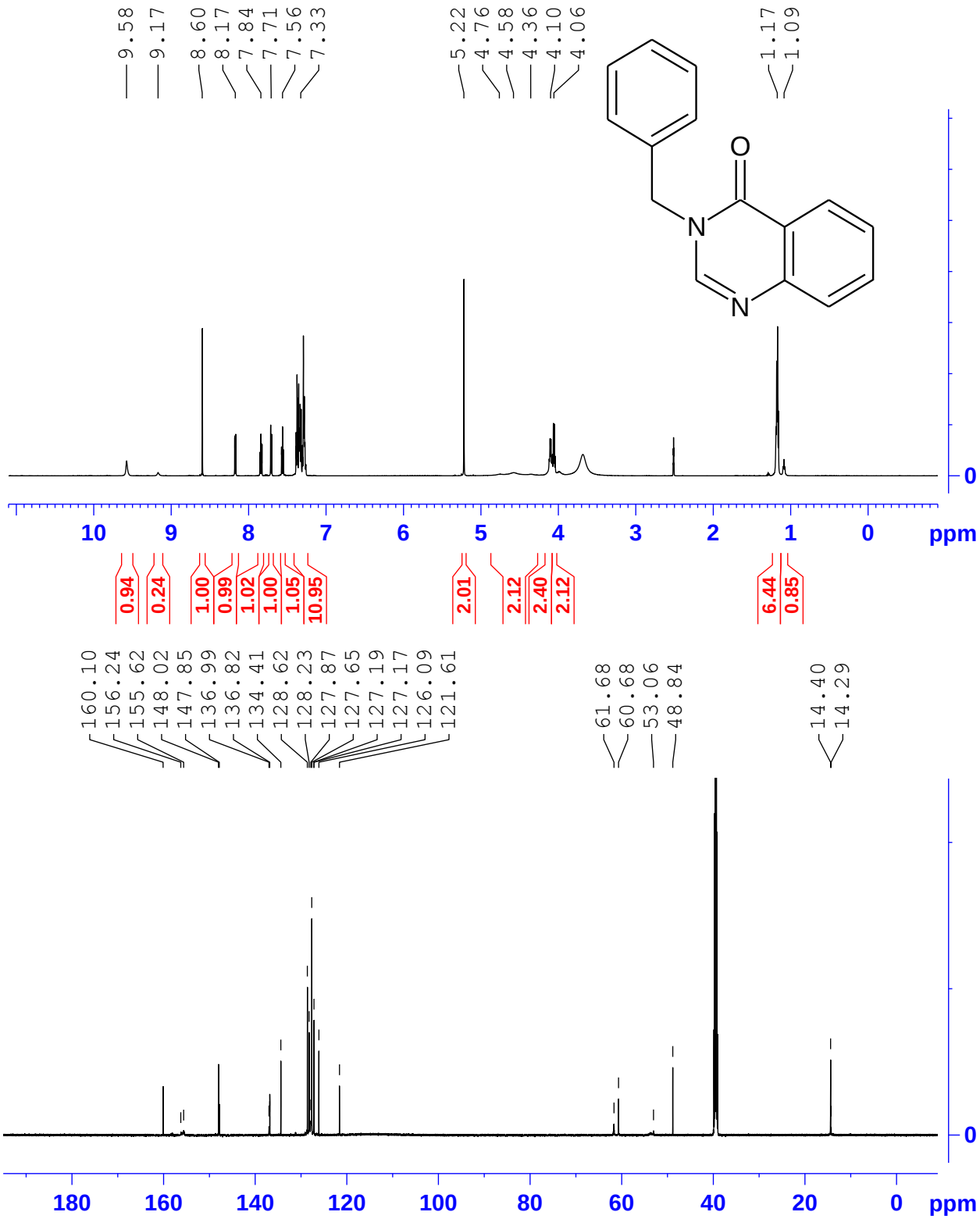
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8
7
6
5
4
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2.12
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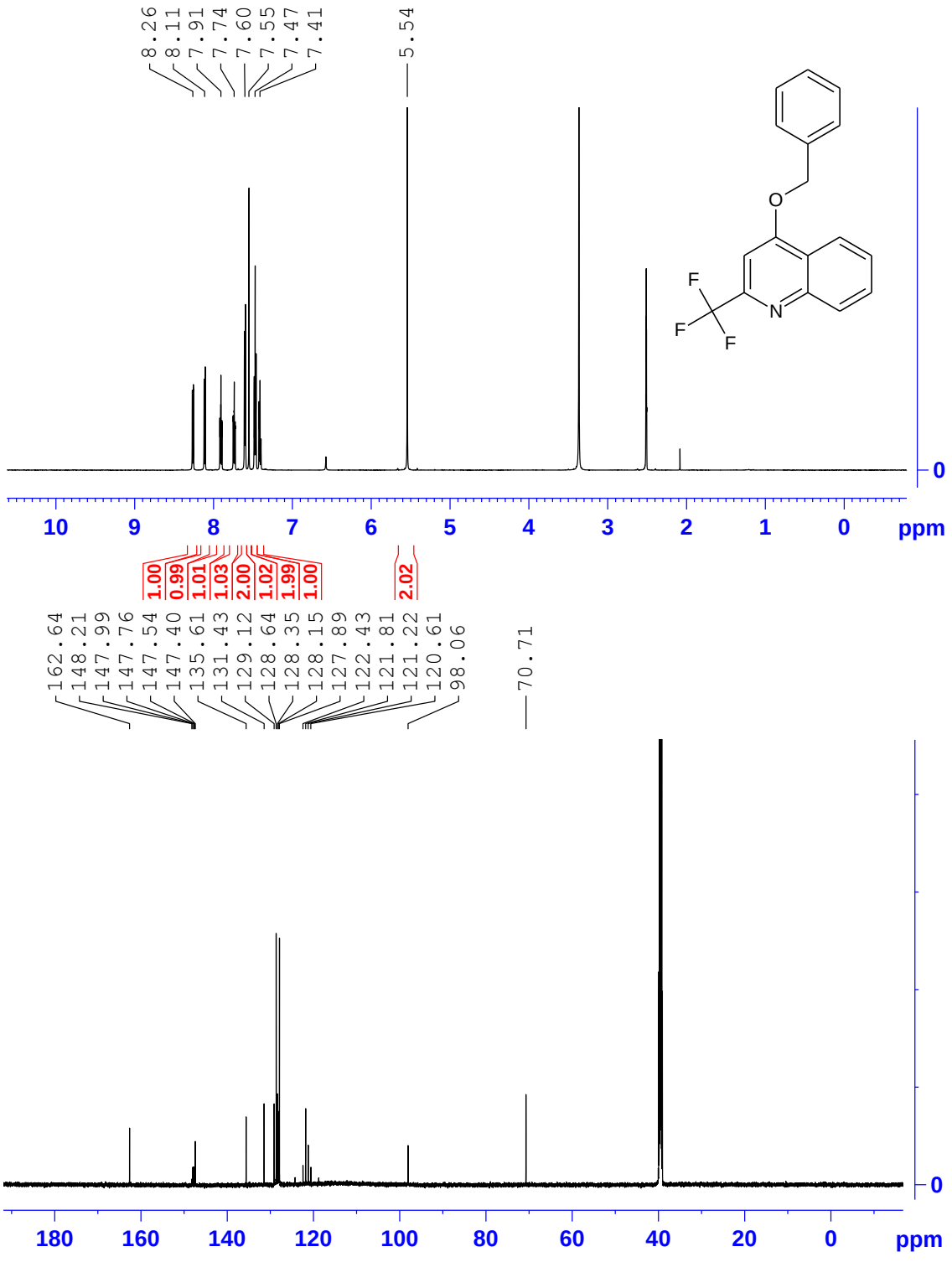
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F
F
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10
9
8
7
6
5
4
3
2
1
0
ppm
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1.01
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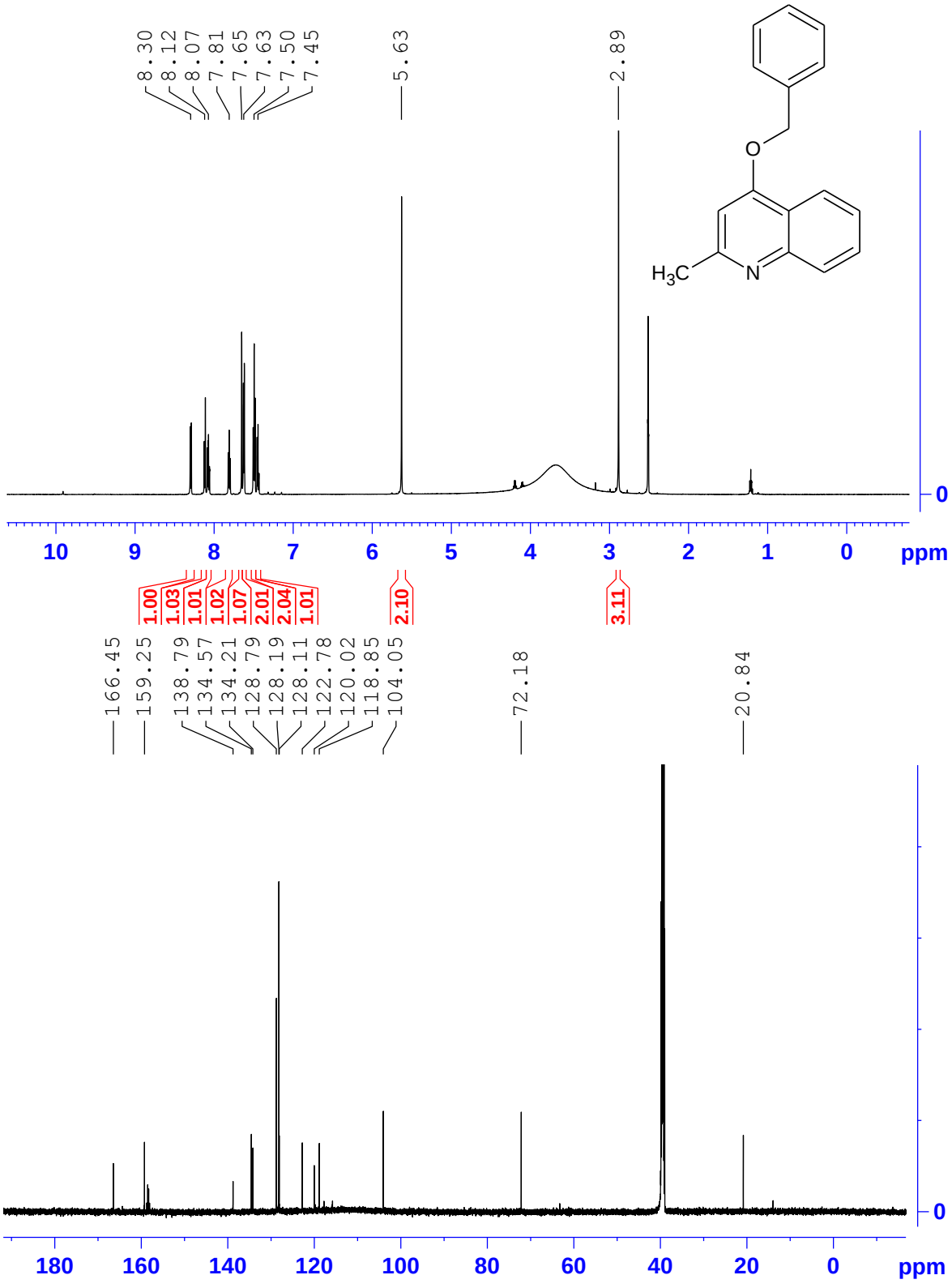
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9
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6
5
4
3
2
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ppm
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1.07
2.01
2.04
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3.11
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20
0
ppm

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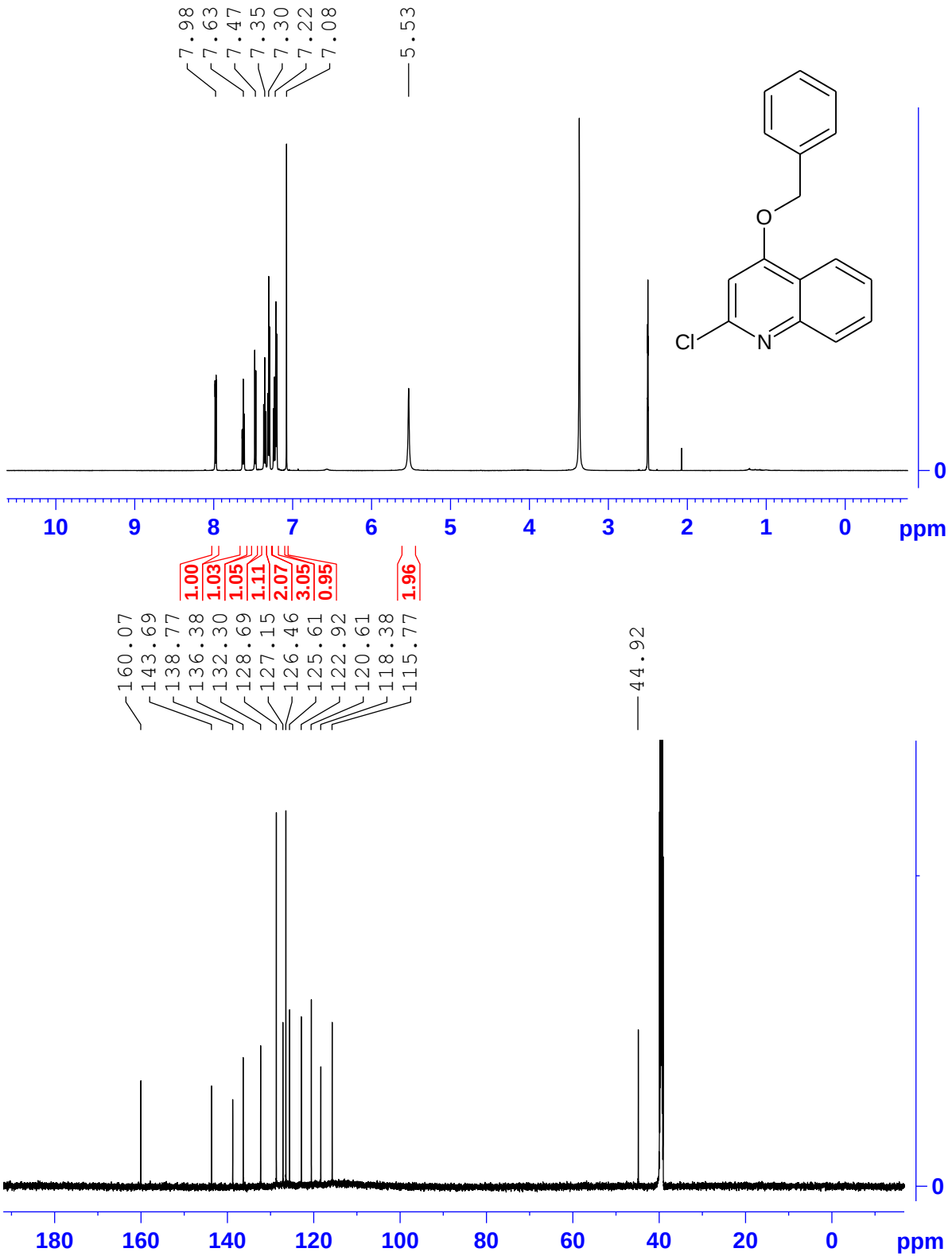
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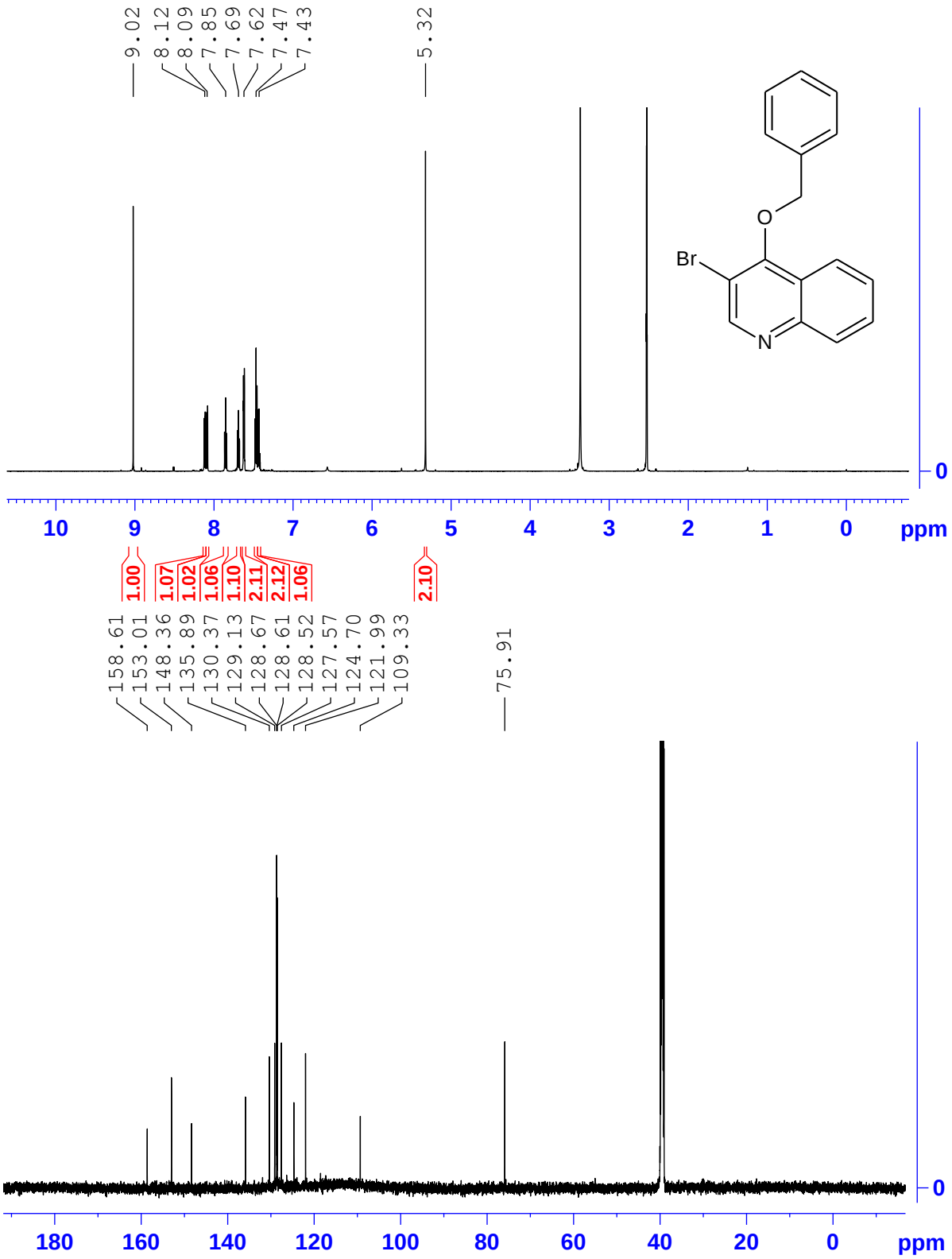
ppm

Compound 11 Major



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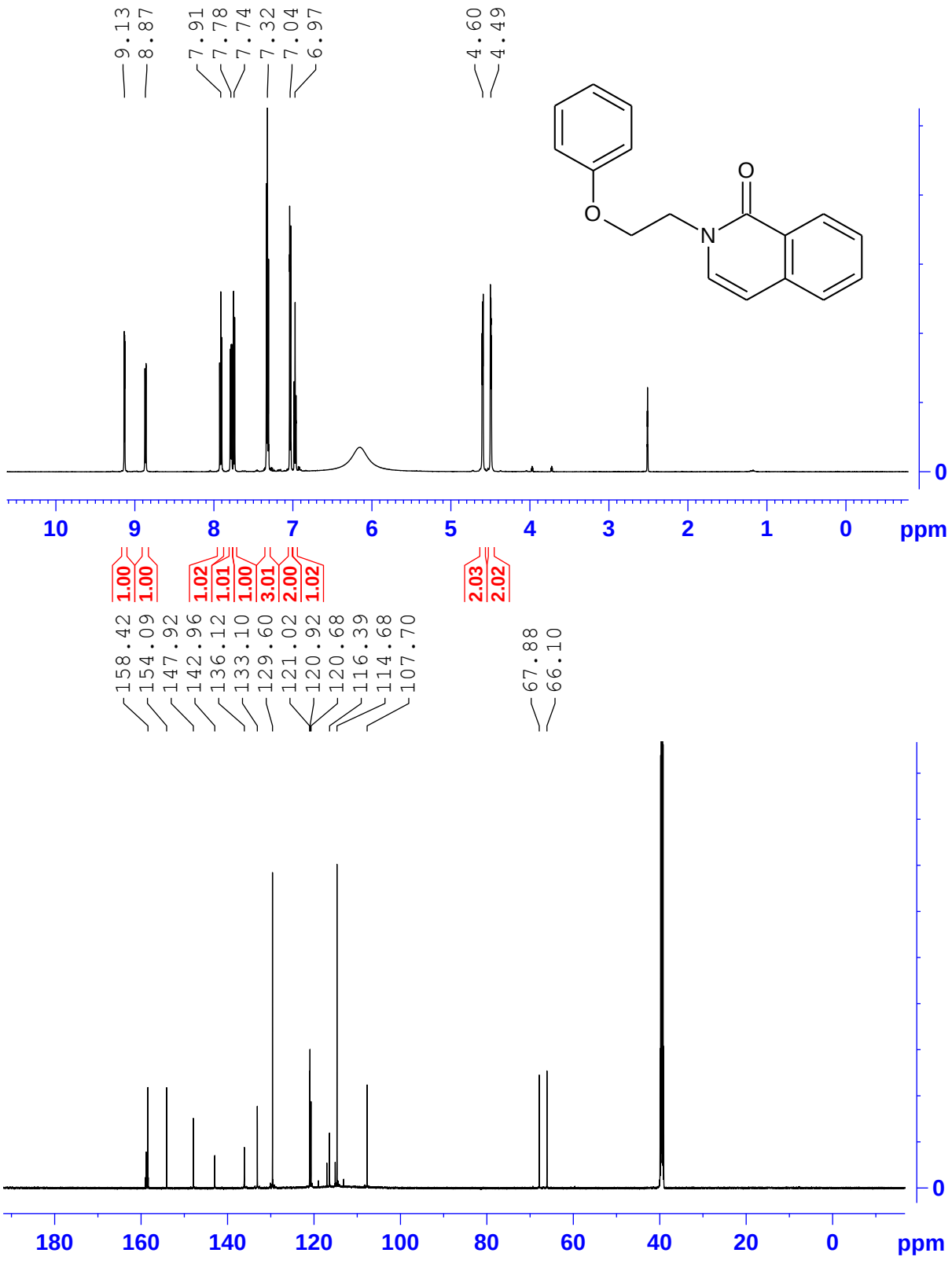
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10
9
8
7
6
5
4
3
2
1
0
ppm
1.00
1.00
1.02
1.01
1.00
3.01
2.00
1.02
2.03
2.02
158.42
154.09
147.92
142.96
136.12
133.10
129.60
121.02
120.92
120.68
116.39
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20
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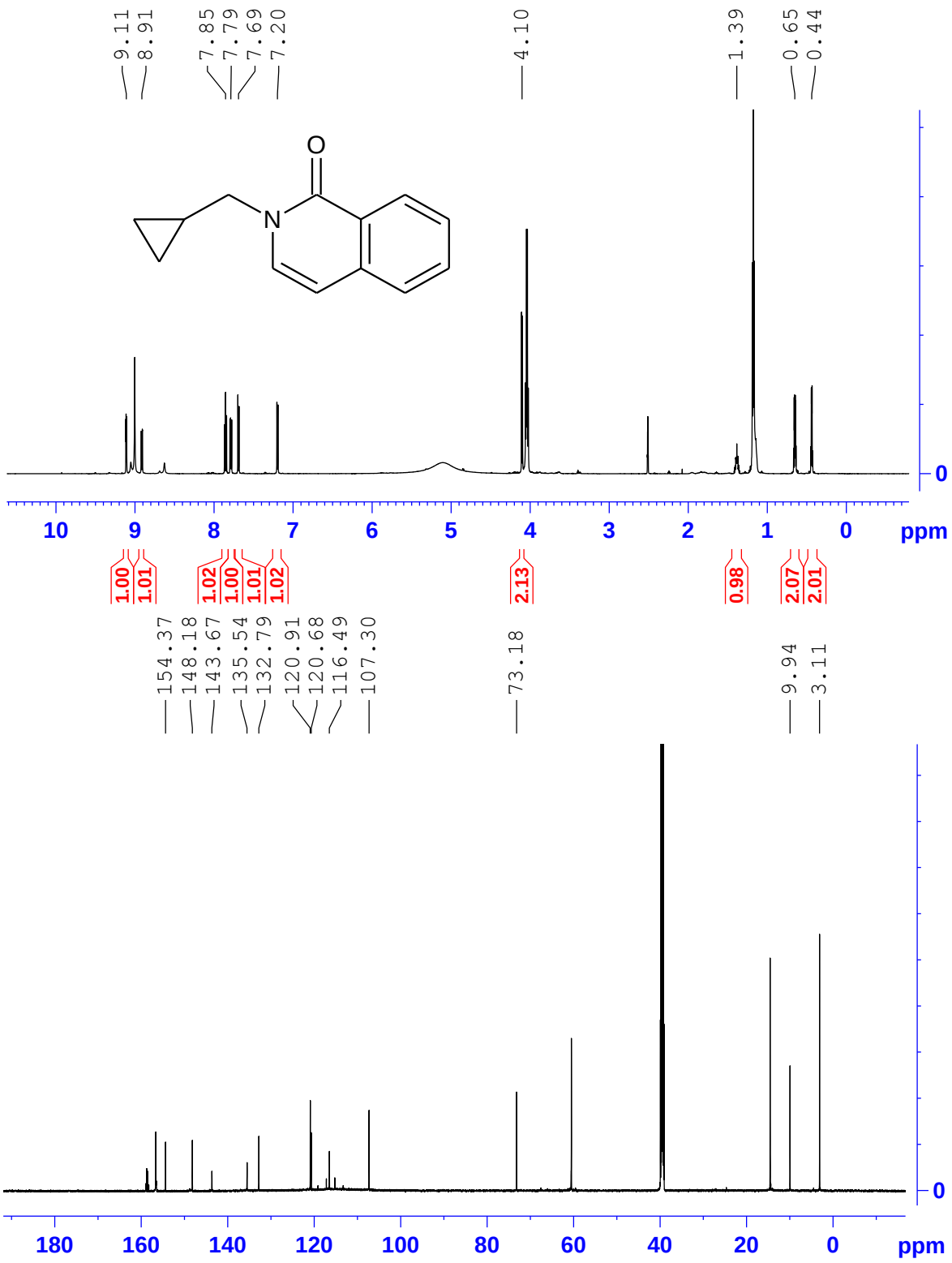
ppm

Compound 15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7
6
5
4
3
2
1
0
ppm
1.00
1.01
1.02
1.00
1.01
1.02
2.13
0.98
2.07
2.01
154.37
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143.67
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132.79
120.91
120.68
116.49
107.30
73.18
9.94
3.11
180
160
140
120
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40
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ppm