Supplementary Material for Organic & Biomolecular Chemistry

Organocatalytic Asymmetric Destruction of 1-Benzylated Reissert Compounds Catalysed by Quaternary Cinchona Alkaloids

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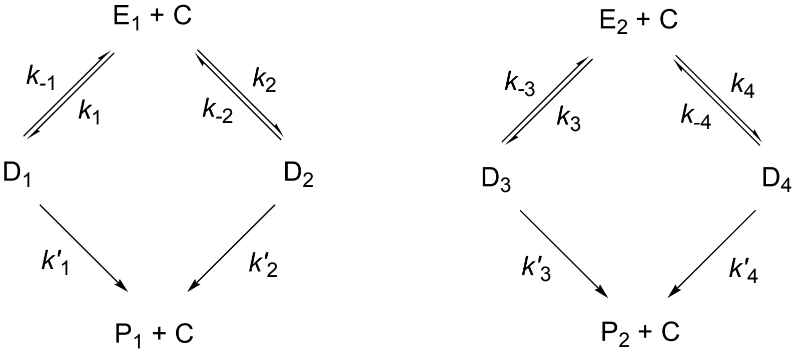
Supporting Information

Derivation of Eq. 2 and the Equation: $\mathrm{er} = \exp((k^{\mathrm{app}}_{\mathrm{fast}} - k^{\mathrm{app}}_{\mathrm{slow}})[\mathrm{C}]t)$ **:**

Consider Scheme S1 below. Here E_x (x = 1,2) are the enantiomers of the substrate (**2**), C is the catalyst with hydroxide as the counter anion ($^*R_4NOH$), D_y (y = 1-4) are the four possible diastereomeric adducts of E_x and C (**7**). P_x are the product α-amino nitriles (**8**).[1]



Scheme S1

The rate expression for E_1 is given by:

$$\frac{d[E_1]}{dt} = k_{-1}[D_1] + k_{-2}[D_2] - (k_1 + k_2)[C][E_1]$$

Assuming steady state conditions for D_1 and D_2:

$$\frac{d[D_1]}{dt} = k_1[C][E_1] - (k_{-1} + k'_1)[D_1] = 0 \Rightarrow [D_1] = \frac{k_1[C][E_1]}{k_{-1} + k'_1}$$

$$\frac{d[D_2]}{dt} = k_2[C][E_1] - (k_{-2} + k'_2)[D_2] = 0 \Rightarrow [D_2] = \frac{k_2[C][E_1]}{k_{-2} + k'_2}$$

Then,

$$\frac{d[E_1]}{dt} = \left(\frac{k_{-1}k_1}{k_{-1} + k'_1} + \frac{k_{-2}k_2}{k_{-2} + k'_2} - k_1 - k_2\right)[C][E_1] = -\left(\frac{k_1 k'_1}{k_{-1} + k'_1} + \frac{k_2 k'_2}{k_{-2} + k'_2}\right)[C][E_1]$$

Assuming that $k_{-1} >> k'_1$ and $k_{-2} >> k'_2$ (Michaelis-Menten conditions):

$$\frac{d[E_1]}{dt} = -(k'_1 K_1 + k'_2 K_2)[C][E_1]$$

where $K_1 = k_1/k_{-1}$ and $K_2 = k_2/k_{-2}$.[1]

Since [C] is constant, integration yields:

$$\ln([E_1]/[E_1]_0) = -(k'_1 K_1 + k'_2 K_2)[C]t \qquad \text{eq. S1}$$

where $[E_1]_0$ is the initial concentration of E_1 and t is time.

A similar derivation may be done for E_2:

$$\ln([E_2]/[E_2]_0) = -(k'_3 K_3 + k'_4 K_4)[C]t \qquad \text{eq. S2}$$

where $[E_2]_0$ is the initial concentration of E_2.

Assuming that E_1 is the fastest reacting enantiomer and that we are starting with a racemate, division of eq. S1 by eq. S2, followed by rewriting,[2] we arrive at eq. S3 (*i.e.* eq. 2 in the main paper):

$$\frac{\ln([E_1]/[E_1]_0)}{\ln([E_2]/[E_2]_0)} = \frac{(k'_1 K_1 + k'_2 K_2)}{(k'_3 K_3 + k'_4 K_4)}$$

$$\frac{\ln((1-\text{conv})(1-\text{ee}))}{\ln((1-\text{conv})(1+\text{ee}))} = \frac{k_{\text{fast}}^{\text{app}}}{k_{\text{slow}}^{\text{app}}} = s \qquad \text{eq. S3}$$

where “conv” is the conversion of the reaction ($\text{conv} = \frac{[E_1]+[E_2]}{[E_1]_0 + [E_2]_0}$), ee is the enantiomeric excess of the enriched substrate ($\text{ee} = \frac{[E_2]-[E_1]}{[E_2]+[E_1]}$), $k_{\text{fast}}^{\text{app}} = (k'_1K_1 + k'_2K_2)$ and $k_{\text{slow}}^{\text{app}} = (k'_3K_3 + k'_4K_4)$.

Note that the selectivity factor s is dictated by both the stability (*i.e.* by K_y) and the reactivity (*i.e.* by k'_y) of the intermediate species D_y (y = 1-4).[1]

On the other hand, subtraction of eq. S1 from eq. S2 yields:

$$\ln([E_2]/[E_2]_0) - \ln([E_1]/[E_1]_0) = \ln\left(\frac{[E_2]}{[E_1]}\right) = \ln(er) = (k^{app}_{fast} - k^{app}_{slow})[C]t$$

And thus we arrive at eq. S4:

$$er = \exp((k^{app}_{fast} - k^{app}_{slow})[C]t) \qquad \text{eq. S4}$$

where er is the enantiomeric ratio of the enriched substrate ($[E_2]/[E_1]$).

Determination of Conversions and s-Values

The value of the stereoselectivity factor s was determined according to eq S3. In this equation, “conv” is the conversion of the 1-substituted Reissert compound **2** into the corresponding 1-substituted isoquinoline **3** and ee is the enantiomeric excess of recovered **2**. The conversion and the ee were determined by chiral HPLC from samples collected as described in the experimental section in the main paper. HPLC was applied for the determination of conversion in order to avoid the uncertainty associated with alternative methods such as NMR. The conversion was calculated from the HPLC-data as described below.

Since $n_2 \propto A_2$ and $n_3 \propto A_3$, where n_2 and n_3 are the mols, and A_2 and A_3 are the peak-areas of substrate **2** (both enantiomers) and the product **3**, respectively, the conversion is given by:

$$\mathrm{conv} = \frac{n_3}{n_2 + n_3} = \frac{1}{1 + \frac{n_2}{n_3}} = \frac{1}{1 + \frac{\alpha_2}{\alpha_3}\frac{A_2}{A_3}}$$

The ratio of the proportionality factors α_2/α_3 was determined from samples of known compositions of **2** and **3** (see example in Table S1 and Figures S1 and S2). The value of this ratio depends on the specific HPLC condition (observed wavelength, eluent composition, column, apparatus, *etc.*). HPLC conditions identical to those employed in the determination of the α_2/α_3-ratios were therefore employed when sampling the corresponding catalytic reactions.

n_{2g}/n_{3b}-ratio	A_{2g}/A_{3b}	α_{2g}/α_{3b}
2.0	3.6232	0.5356
2.0	3.8333	
1.5	2.8491	
1.5	2.8640	
1.0	1.8016	
1.0	1.9346	
0.5	0.9558	
0.5	0.9914	
0.2	0.3674	
0.2	0.3996	

Table S1. HPLC-data (two individual experiments) from mixtures of compound **2g** and **3b**.

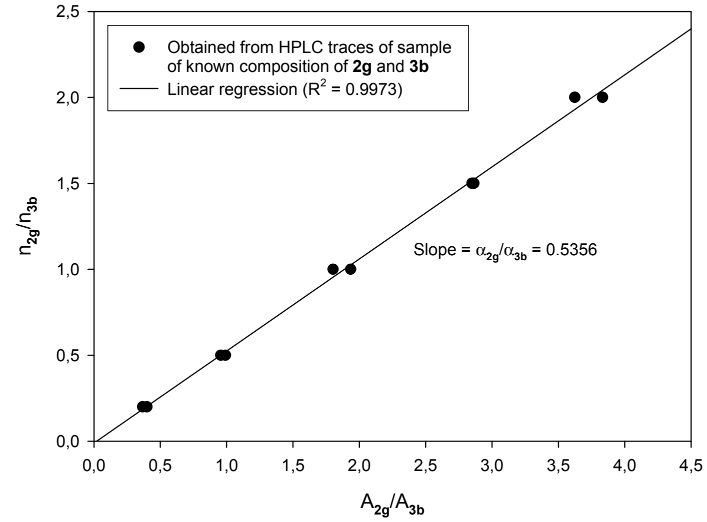
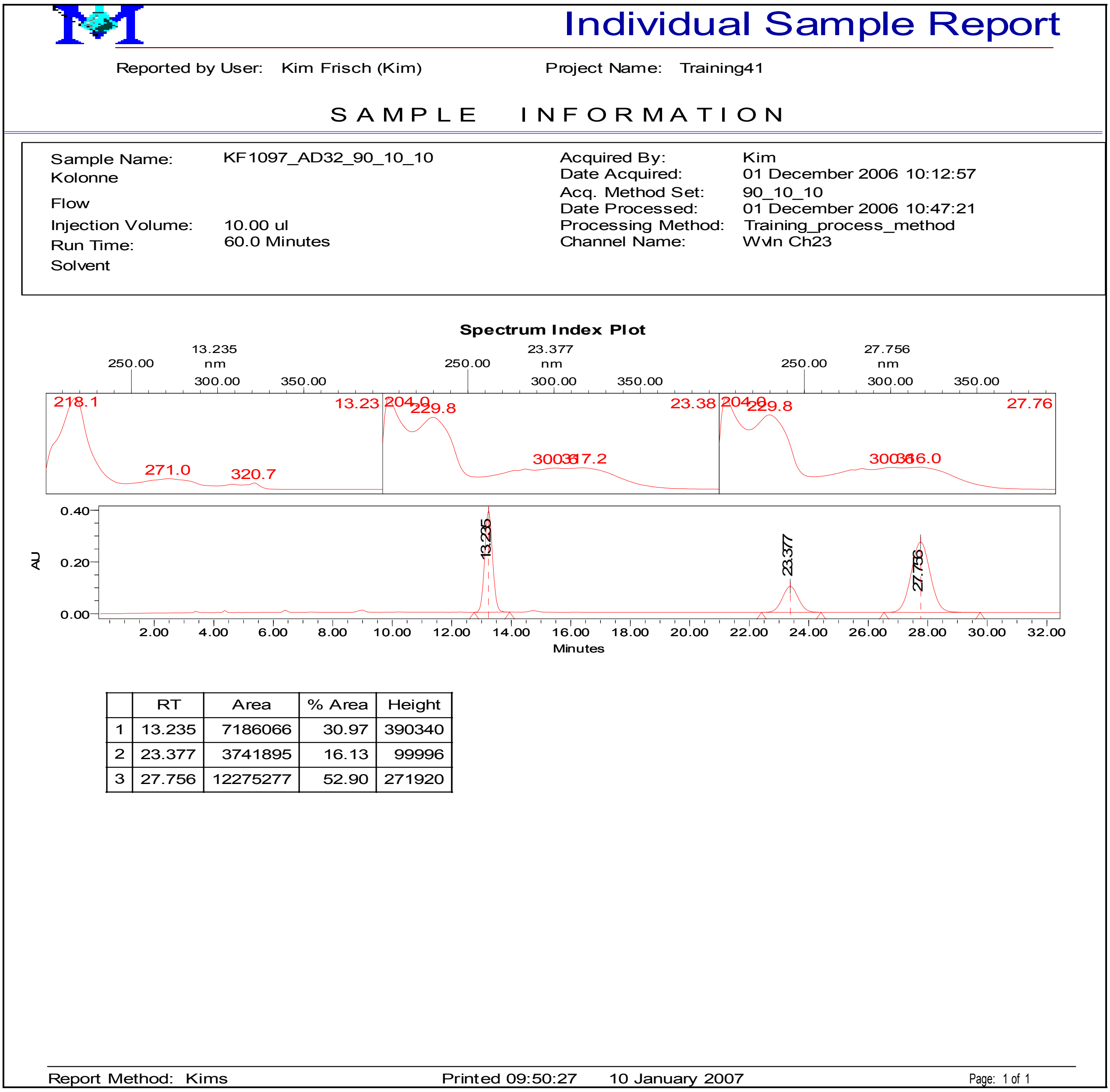


Figure S1. Plot of n_{2g}/n_{3b} *vs.* A_{2g}/A_{3b} recorded from mixtures of compounds **2g** and **3b**.

Figure S2. HPLC-Trace for the Asymmetric Destructions of Reissert Compound **2g** into **3b**

(The chromatogram was recorded at λ = 230 nm).



Individual Sample Report

Reported by User: Kim Frisch (Kim)
Project Name: Training41

SAMPLE INFORMATION

Sample Name:	KF1097_AD32_90_10_10	Acquired By:	Kim
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Flow		Acq. Method Set:	90_10_10
		Date Processed:	01 December 2006 10:47:21
Injection Volume:	10.00 ul	Processing Method:	Training_process_method
Run Time:	60.0 Minutes	Channel Name:	Wvln Ch23
Solvent			

Spectrum Index Plot

	RT	Area	% Area	Height
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2	23.377	3741895	16.13	99996
3	27.756	12275277	52.90	271920

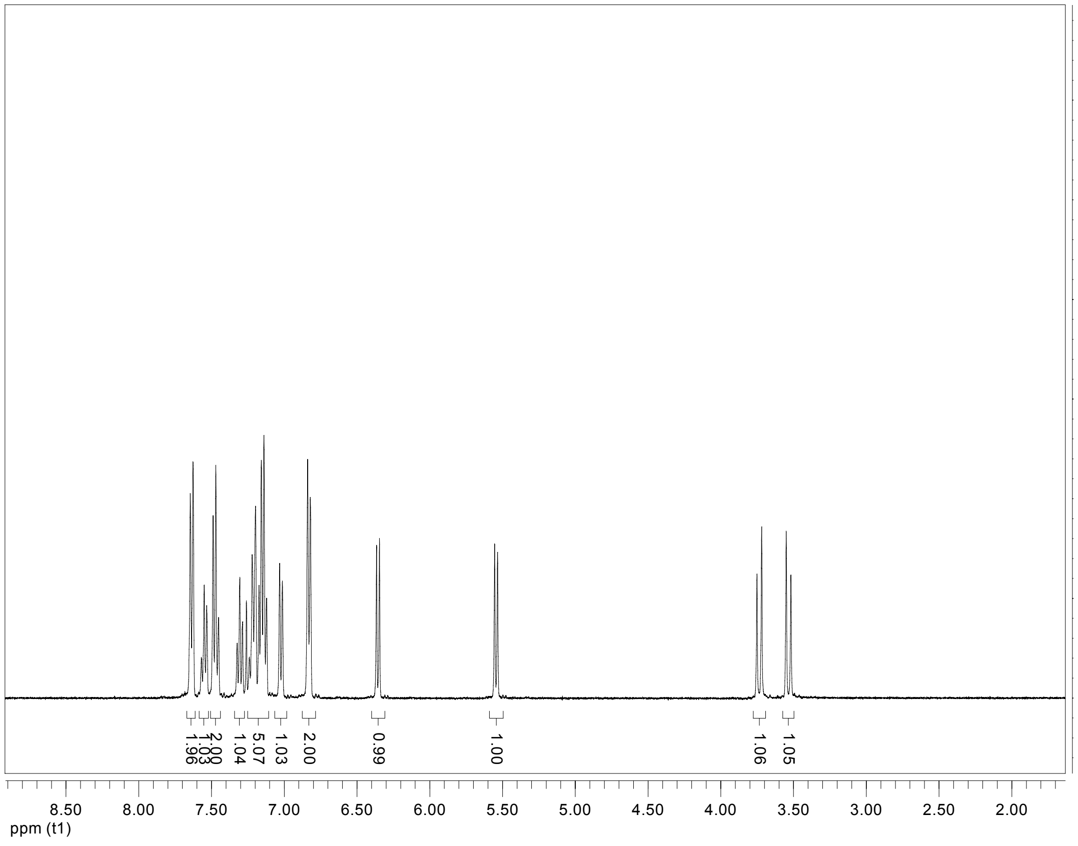
Report Method: Kims
Printed 09:50:27 10 January 2007
Page: 1 of 1

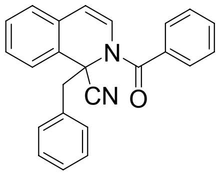
HPLC-conditions: Daicel Chiralpak AD column [hexane/*i*PrOH (90:10)]; flow rate 1.0 mL/min ($\tau_{\mathbf{3b}}$ = 13.3 min.; $\tau_{\mathbf{2g},\mathrm{minor}}$ = 23.4 min.; $\tau_{\mathbf{2g},\mathrm{major}}$ = 27.8 min.).

$\alpha_{\mathbf{2g}}/\alpha_{\mathbf{3b}} = 0.5356$ ($R^2 = 0.9973$)

Results: 45.6% conv.; 53.3% ee; s = 7.5

Copies of ^{1}H and ^{13}C NMR Spectra of Reissert Compounds 2a-k





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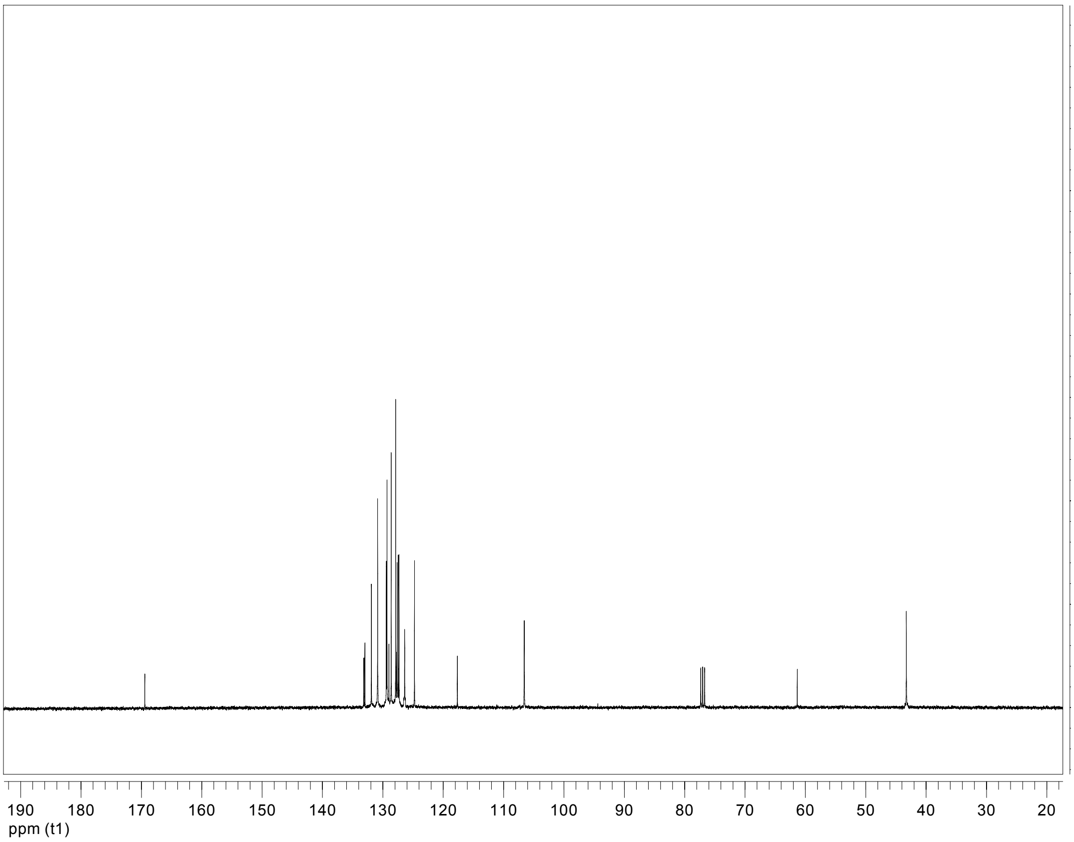
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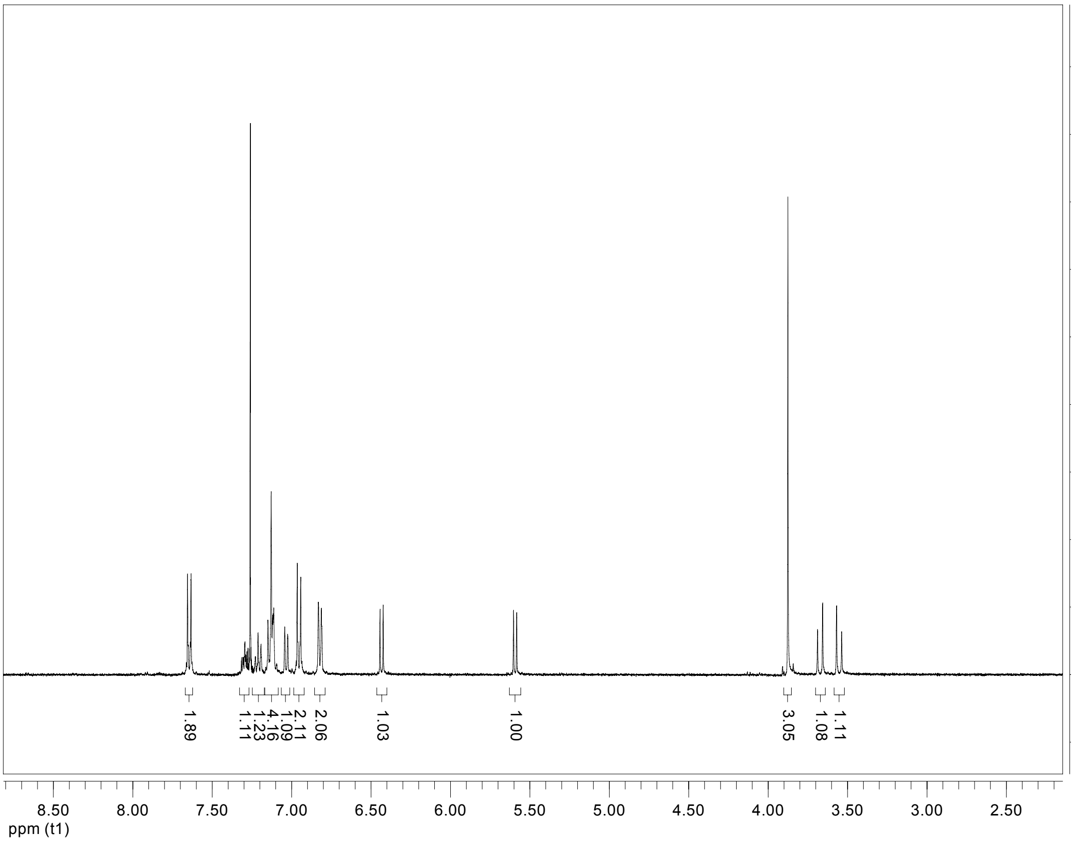
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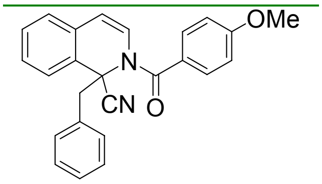
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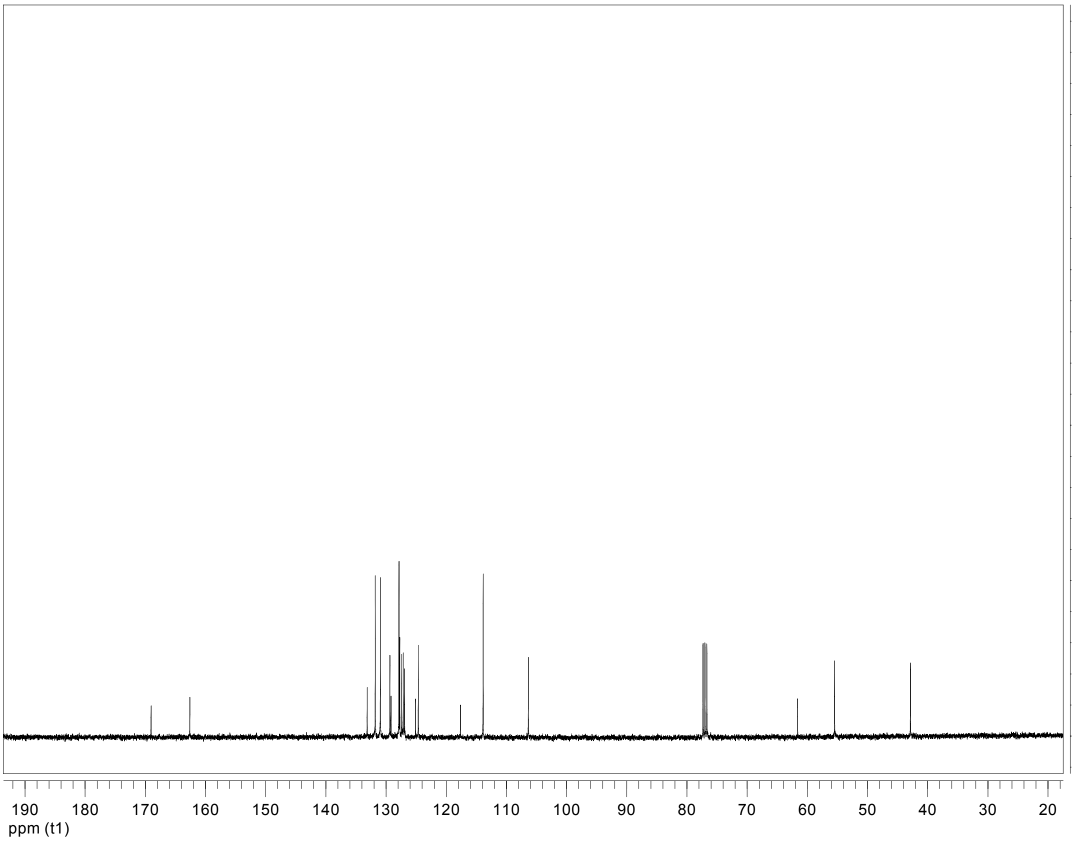
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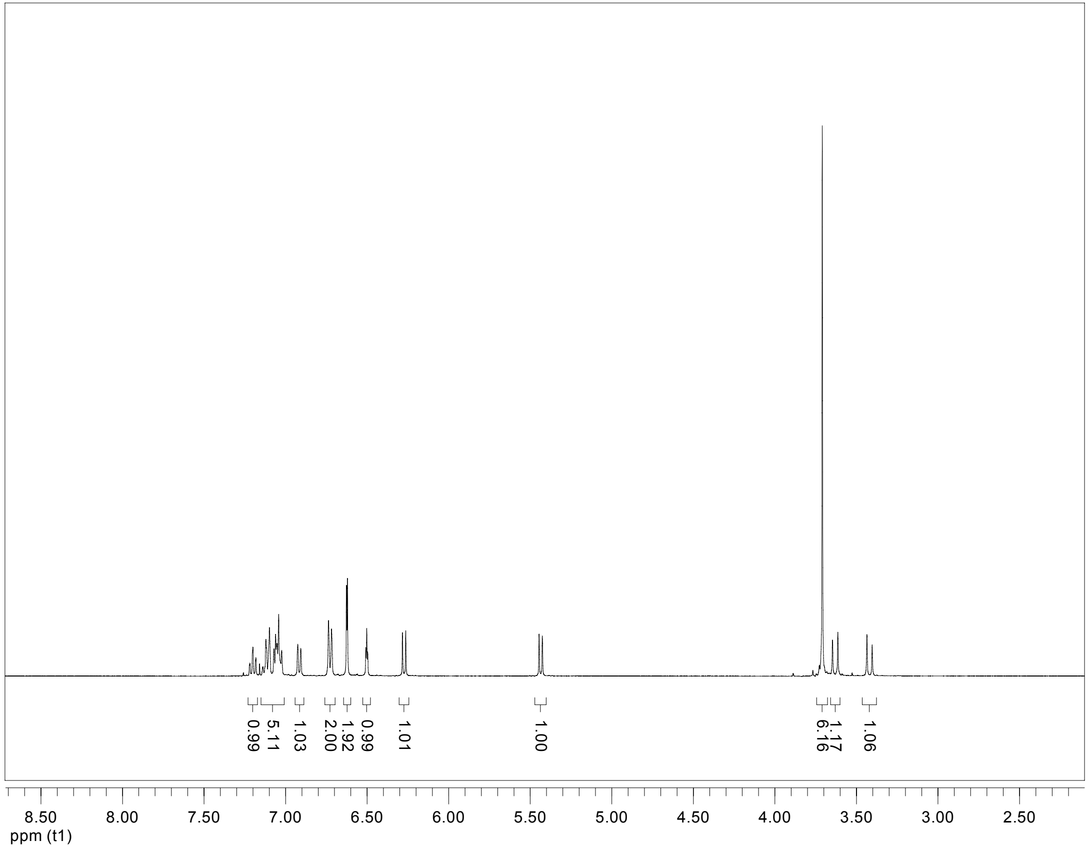
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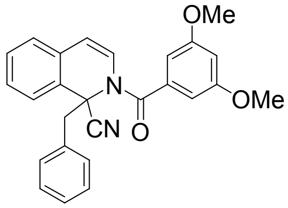
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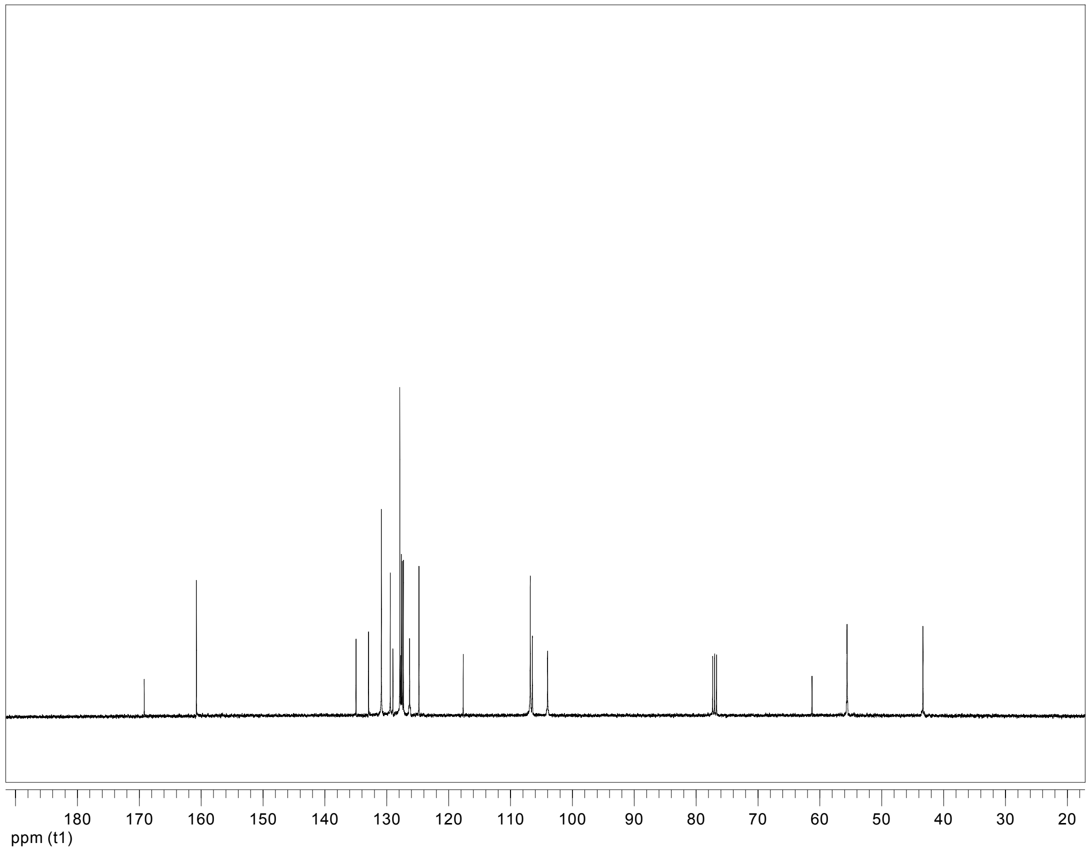
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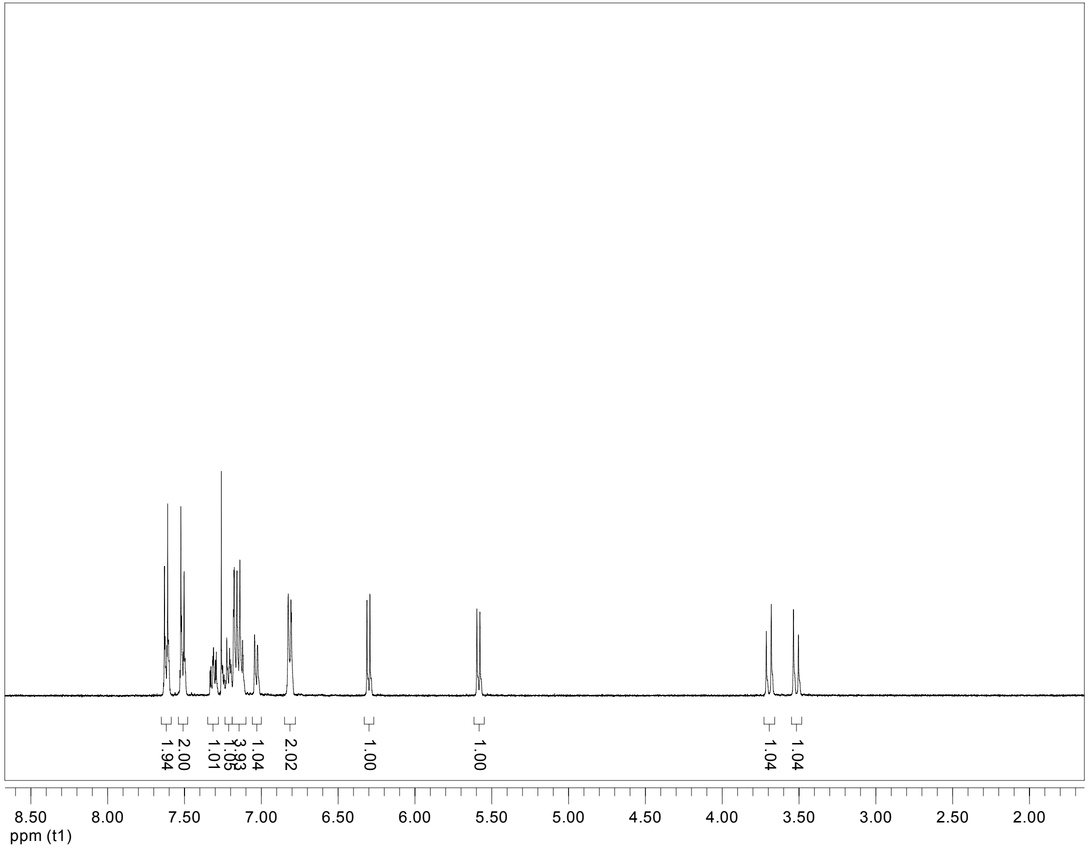
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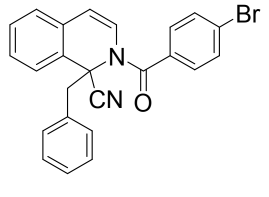
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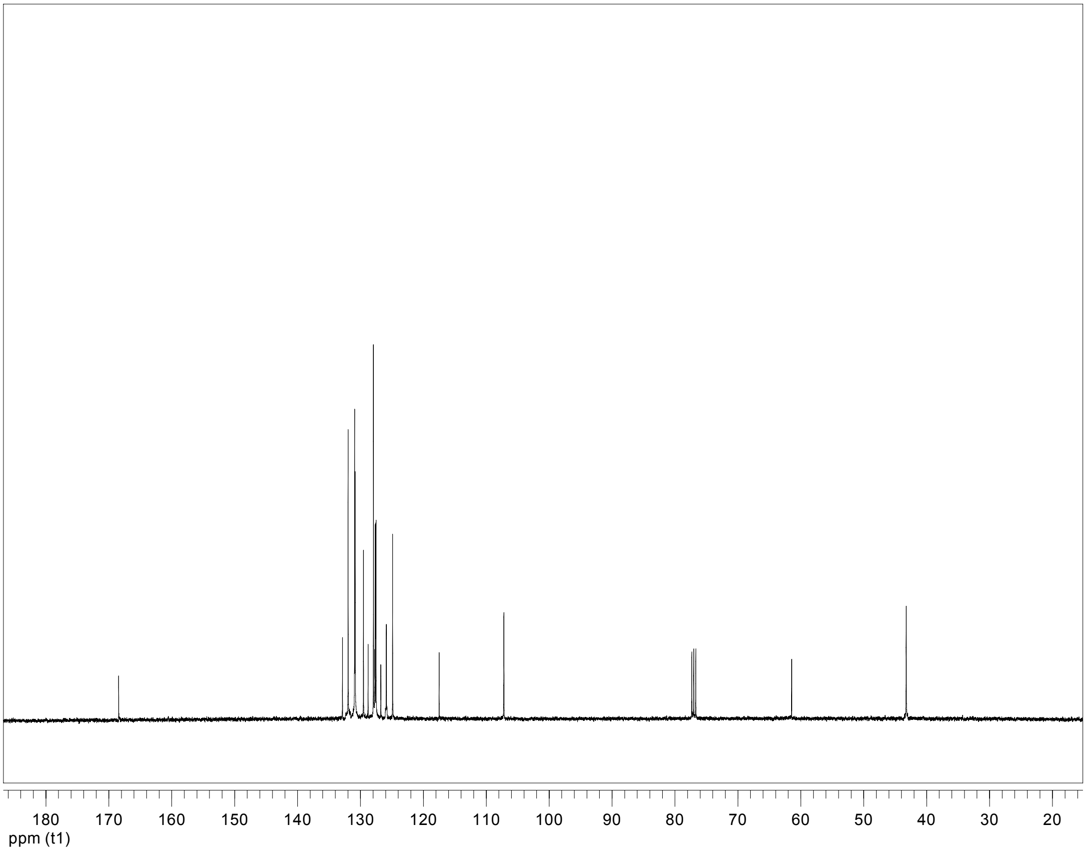
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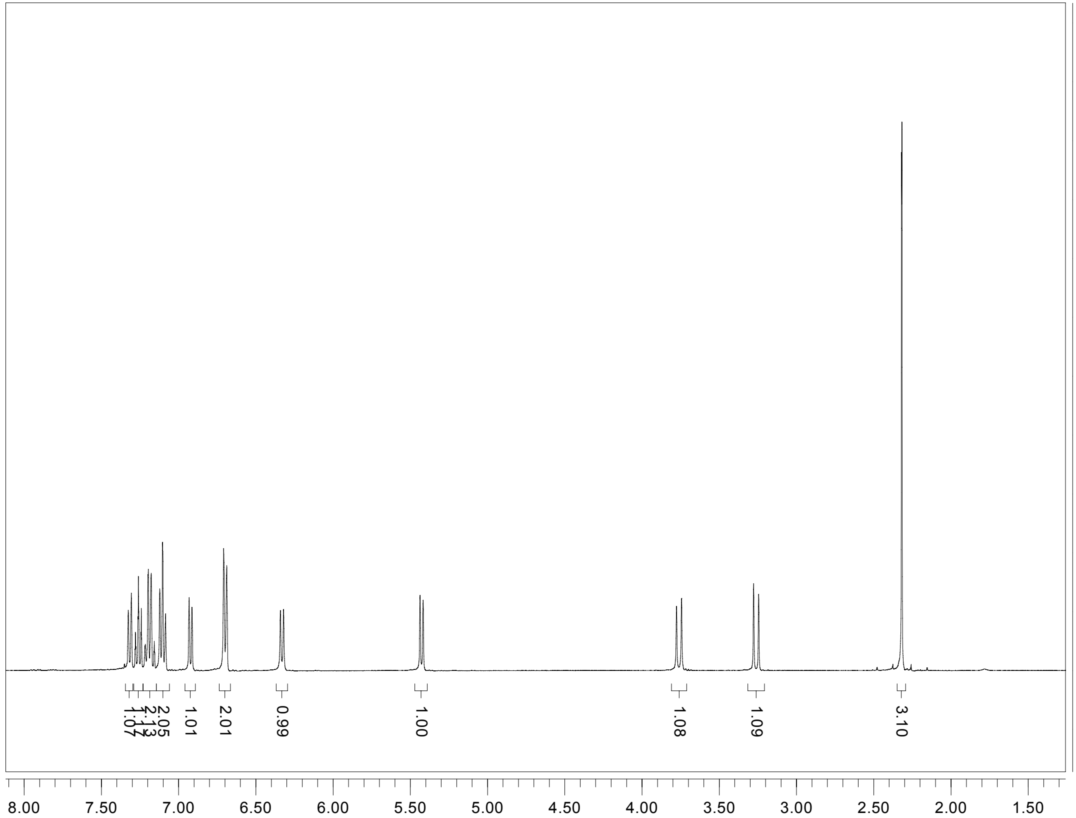
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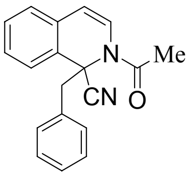
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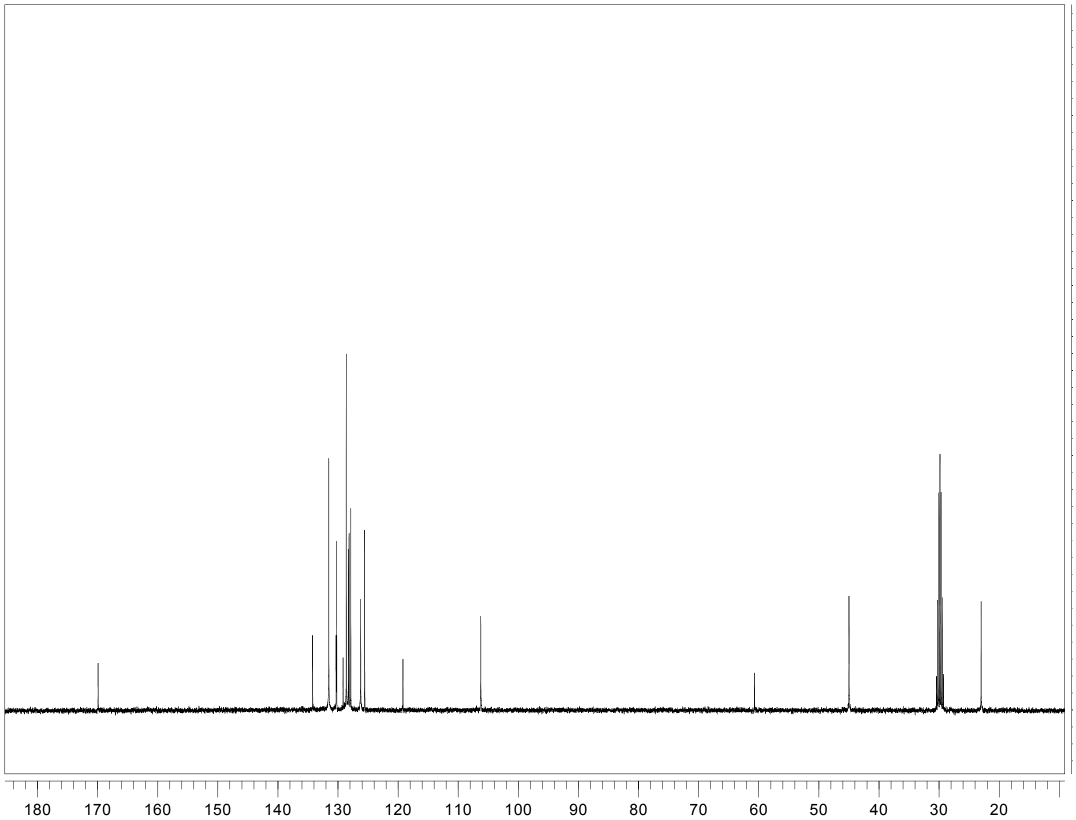
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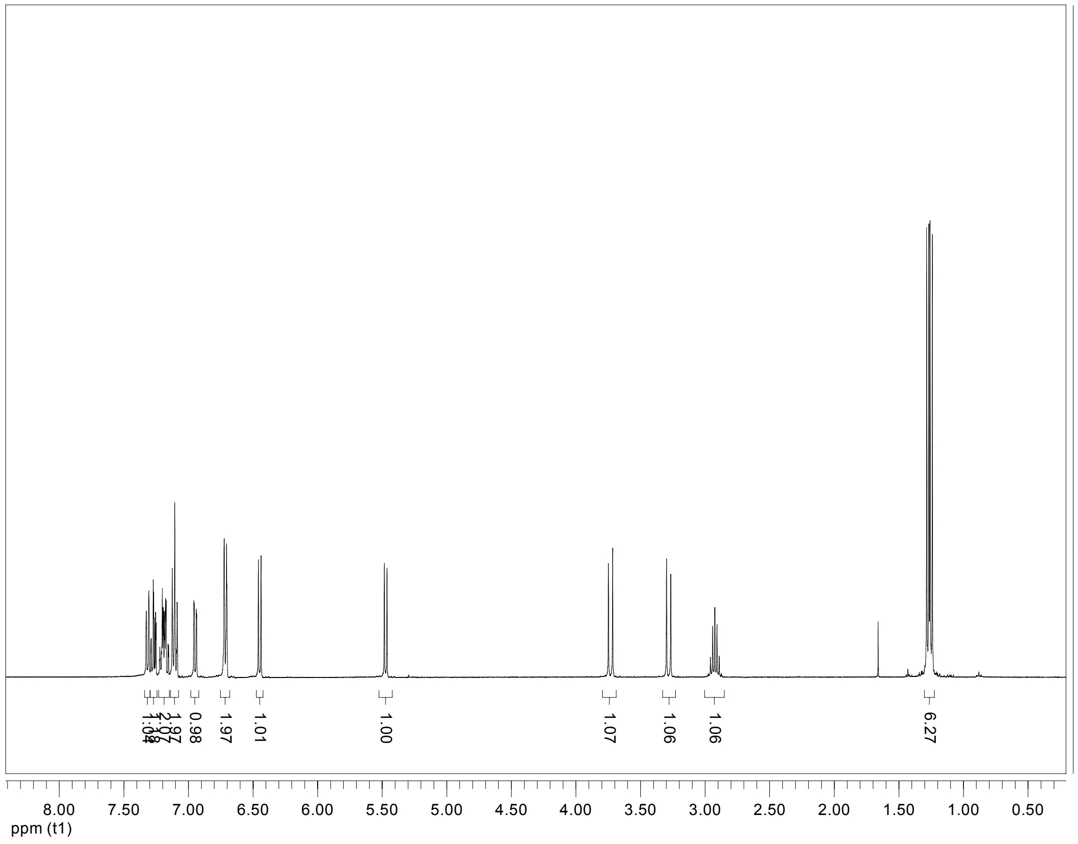
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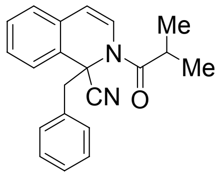
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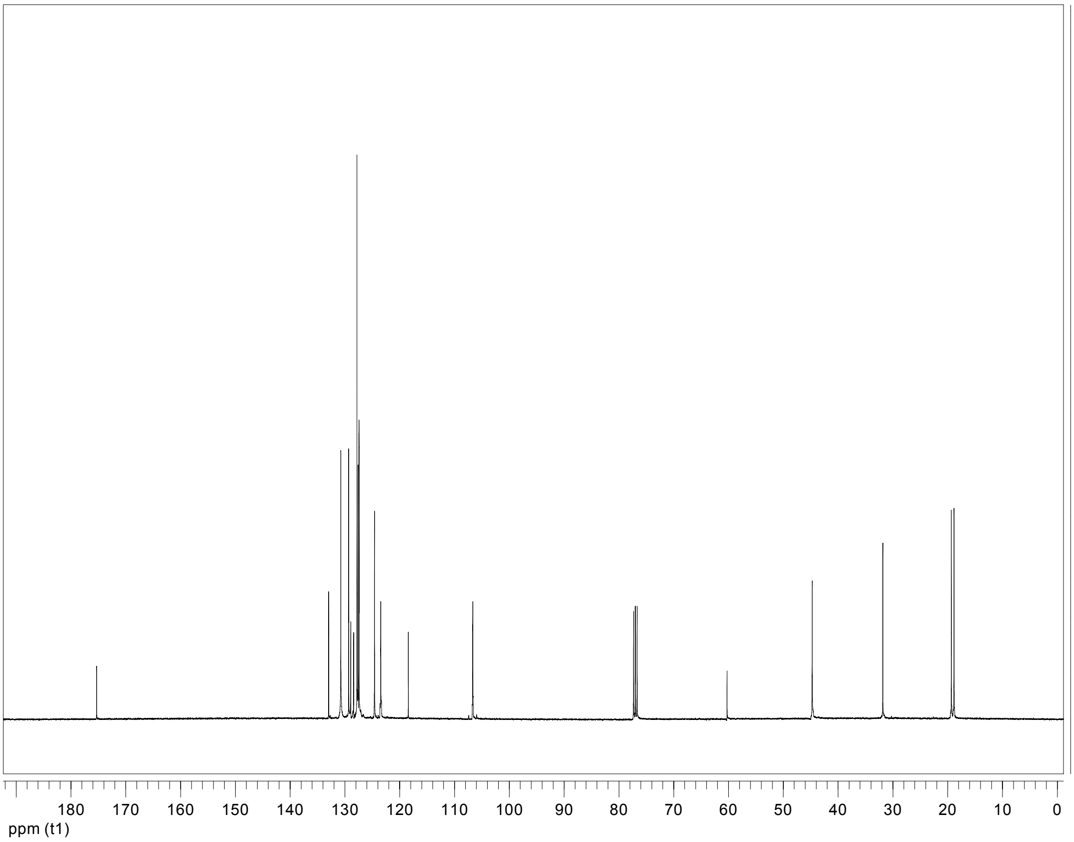
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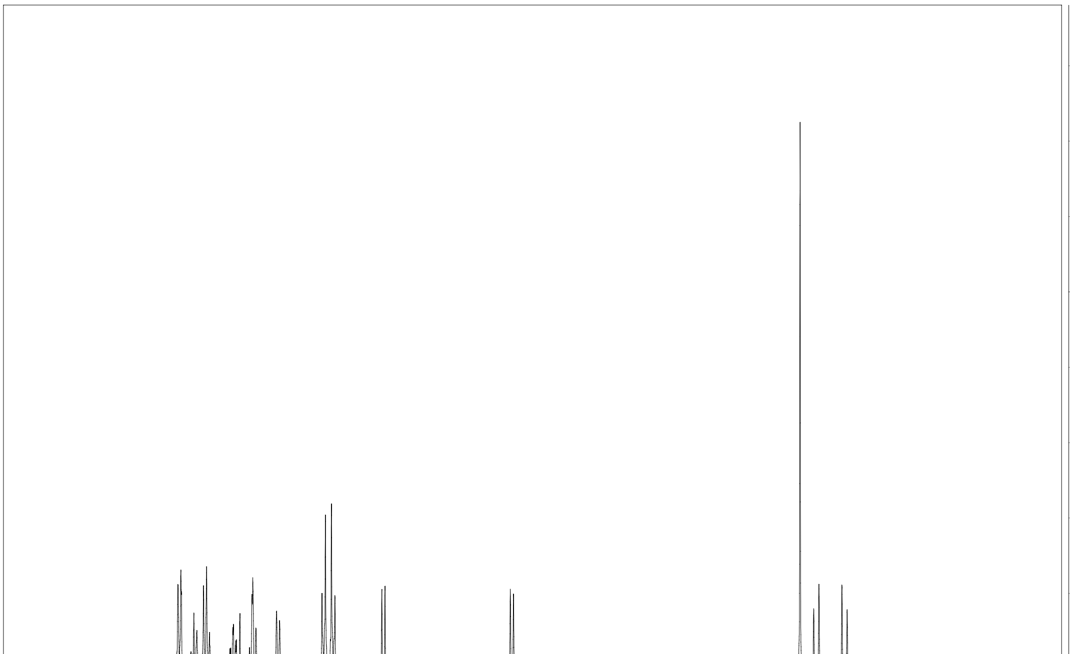
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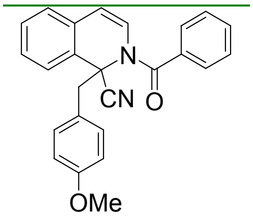
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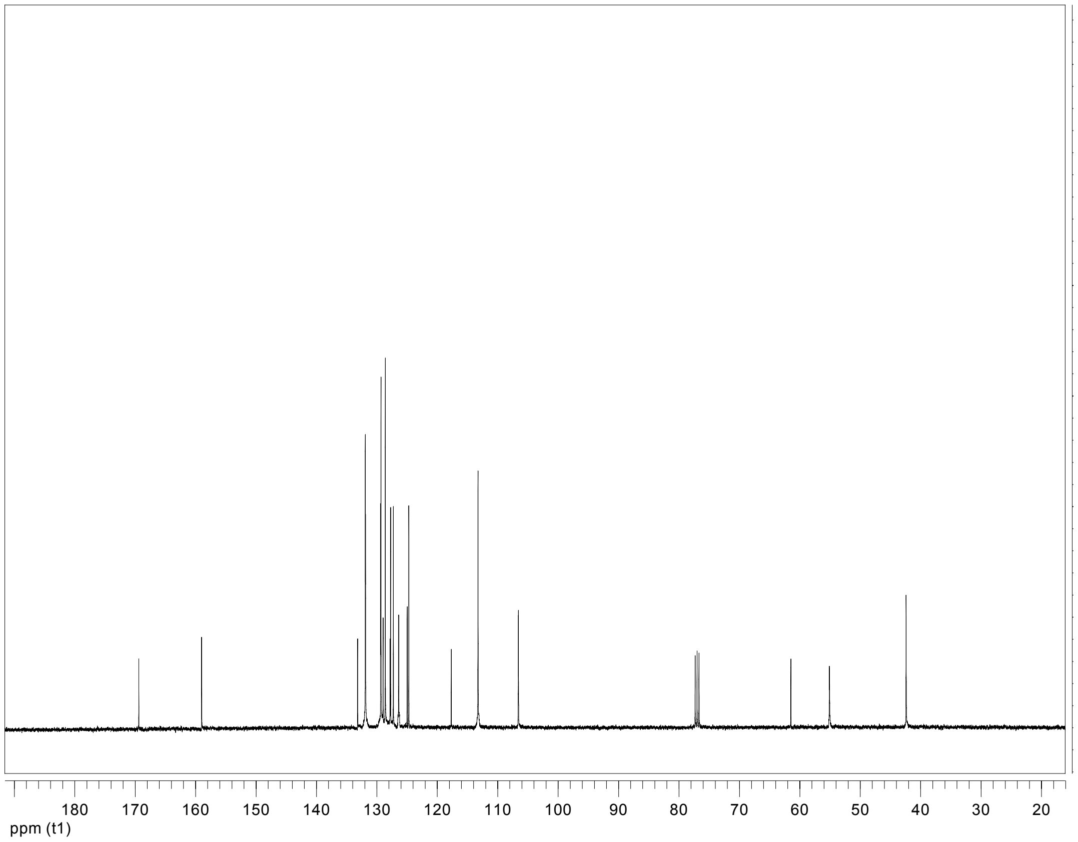
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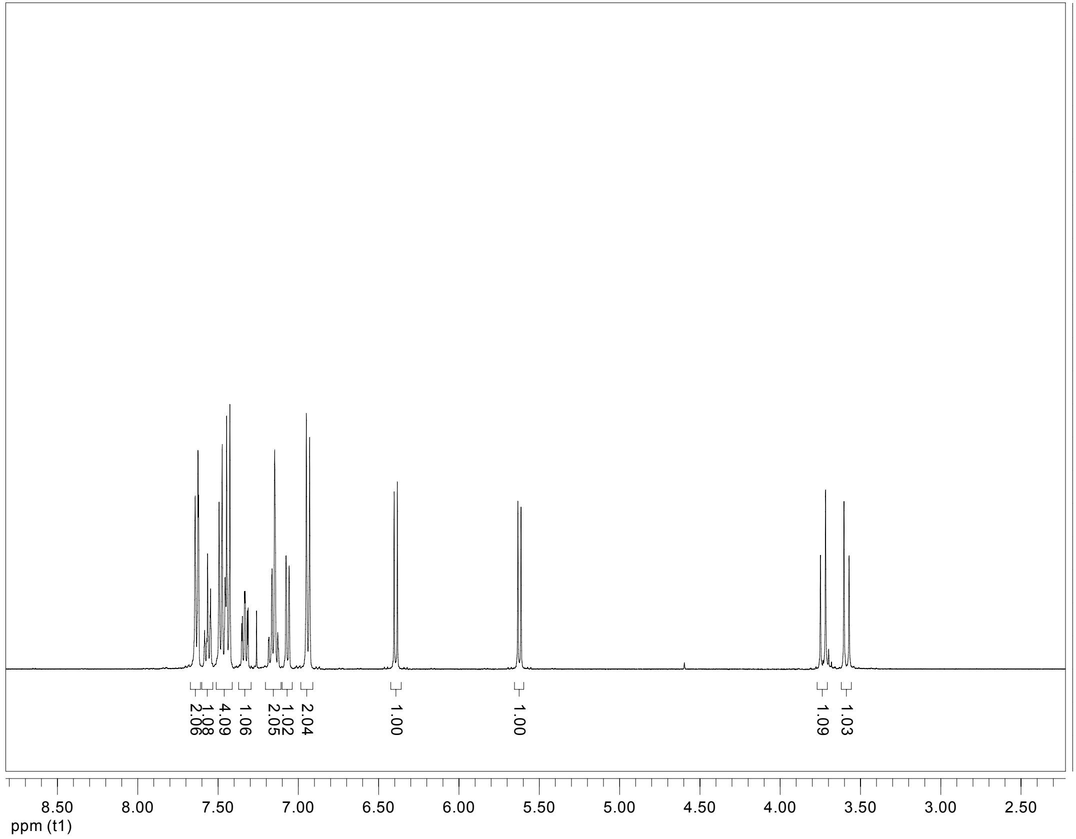
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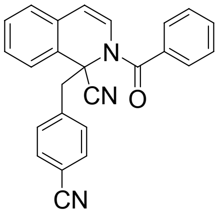
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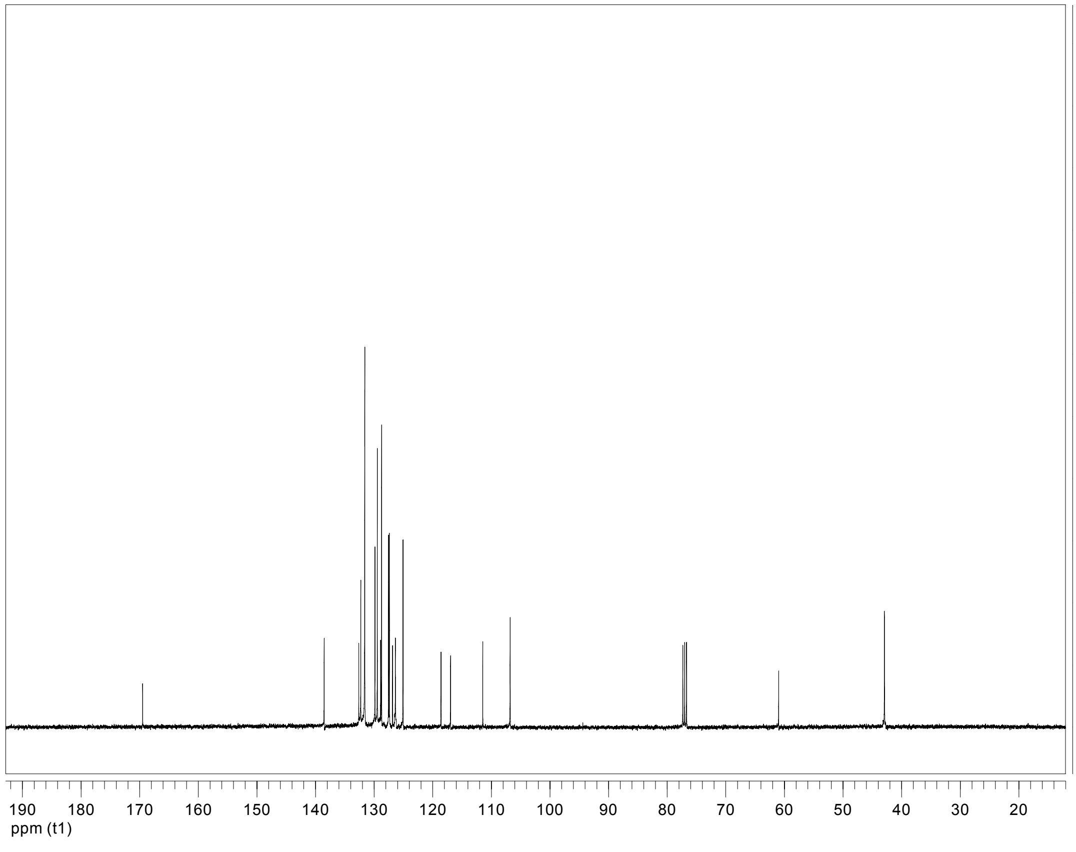
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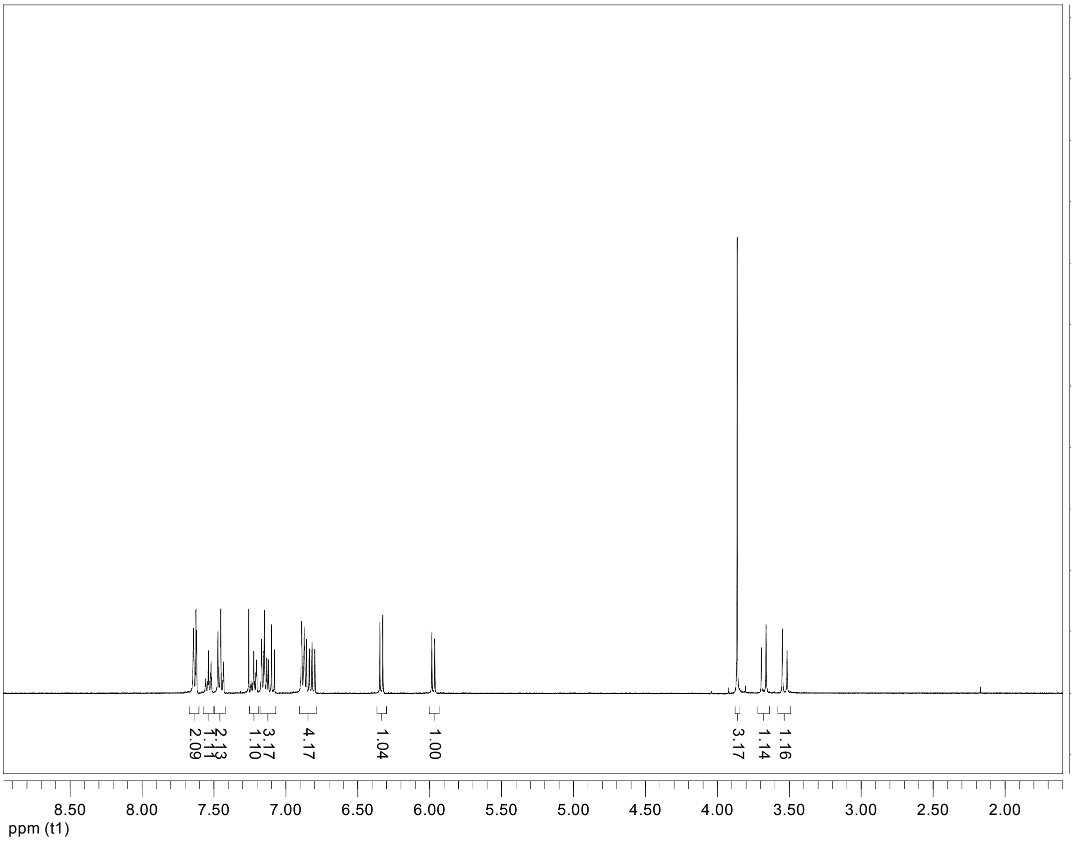
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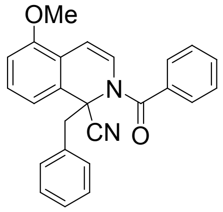
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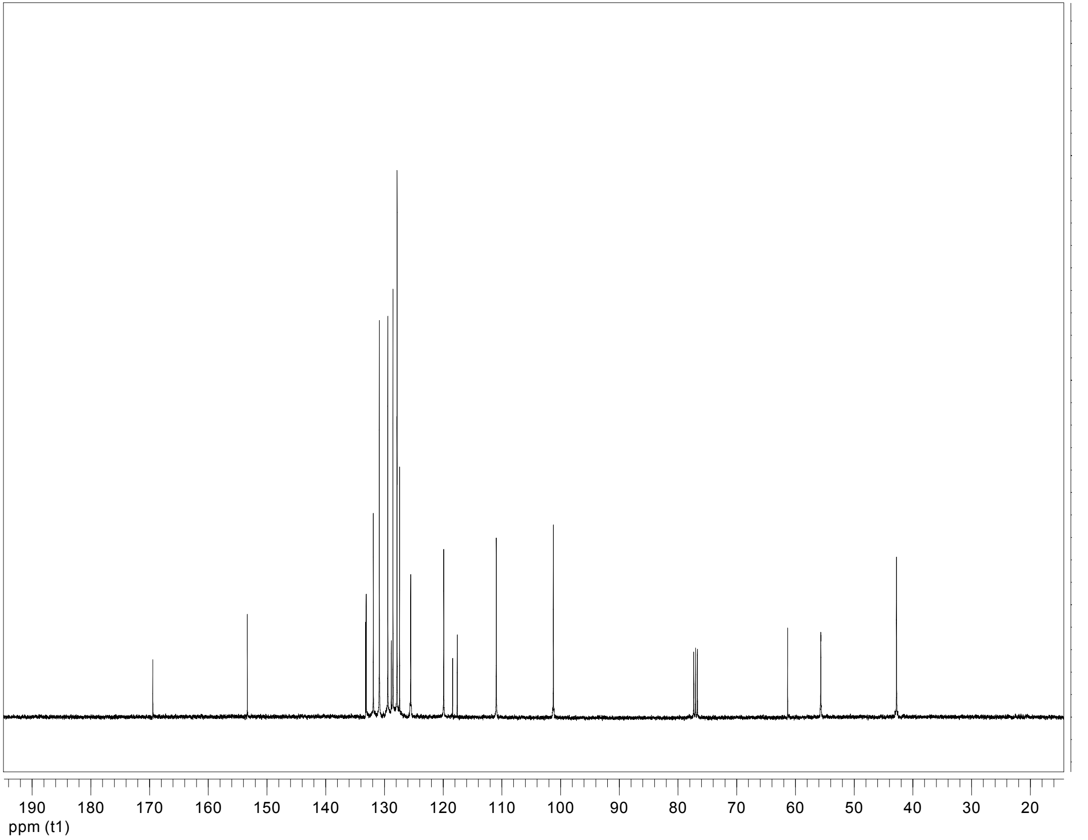
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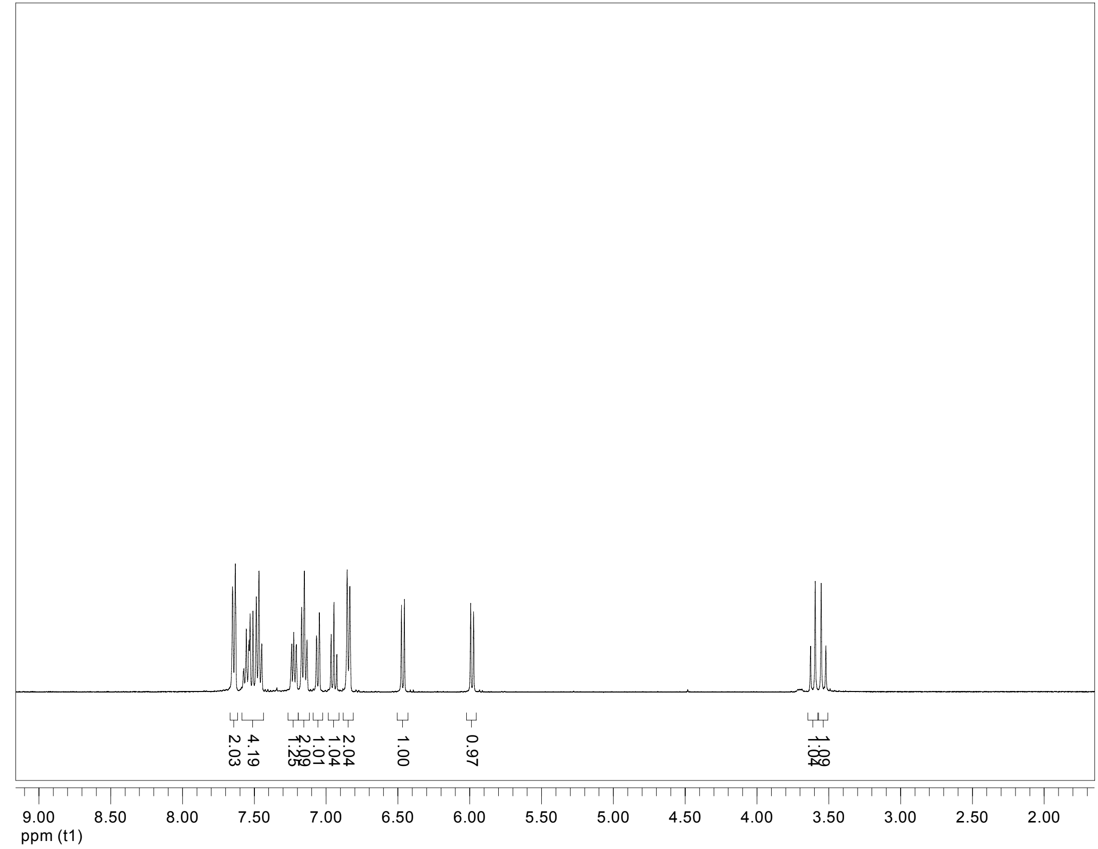
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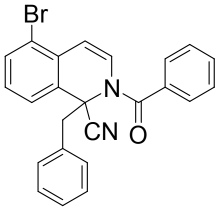
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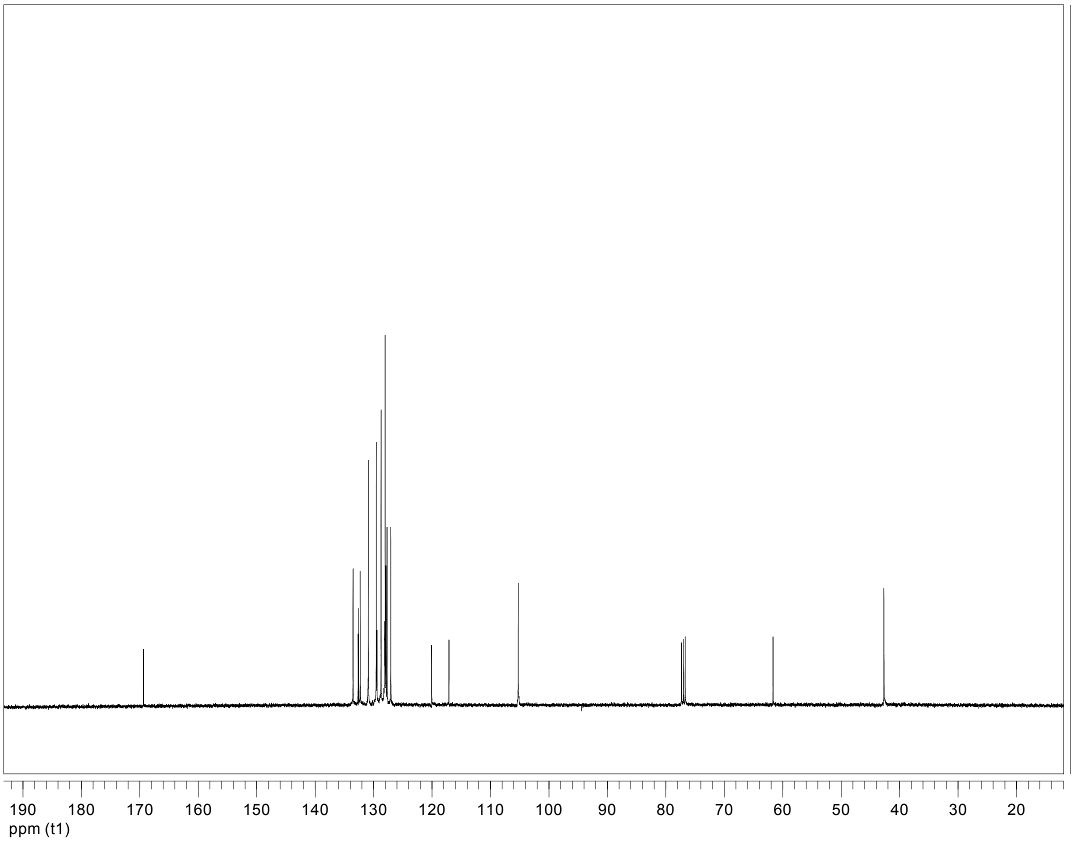
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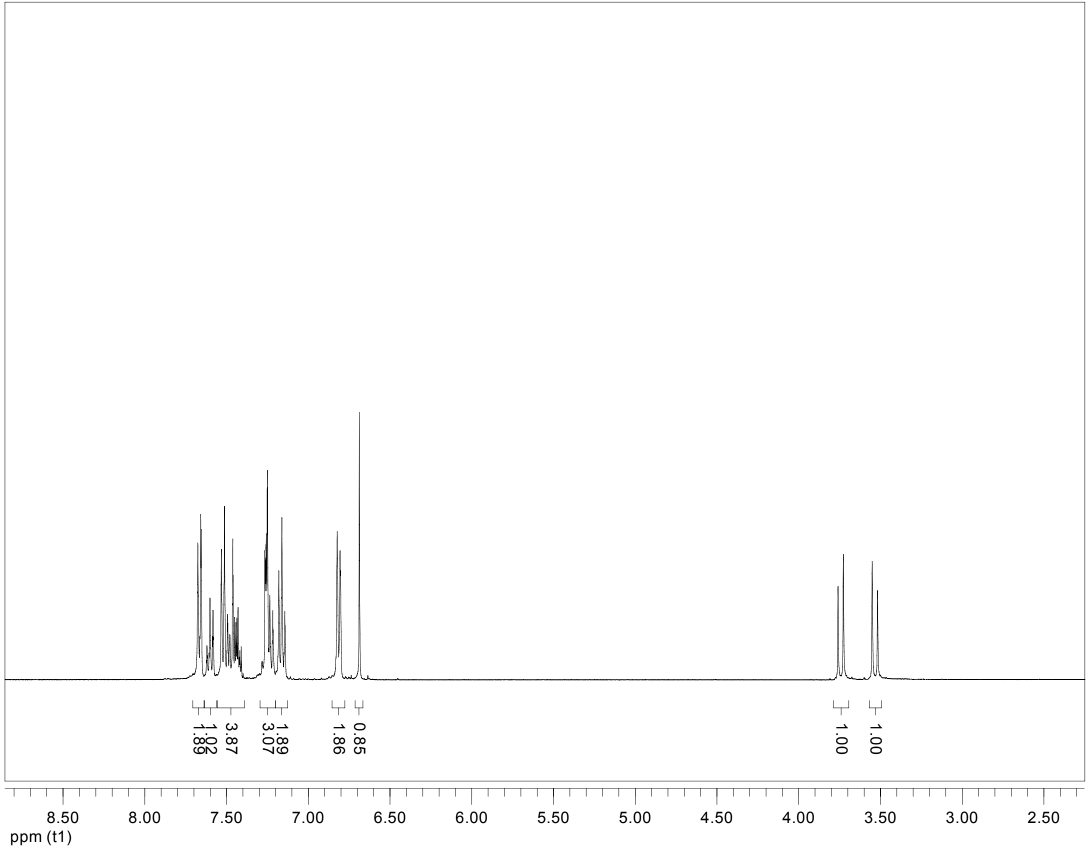
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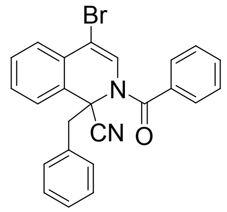
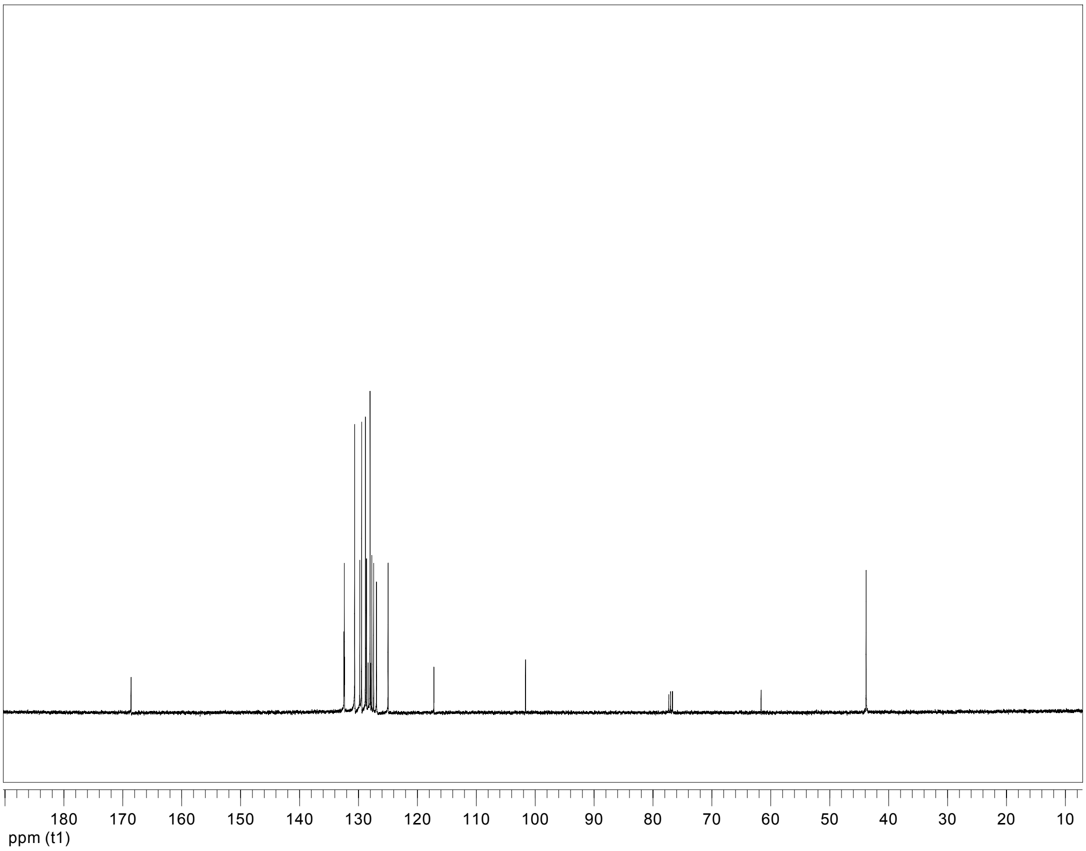
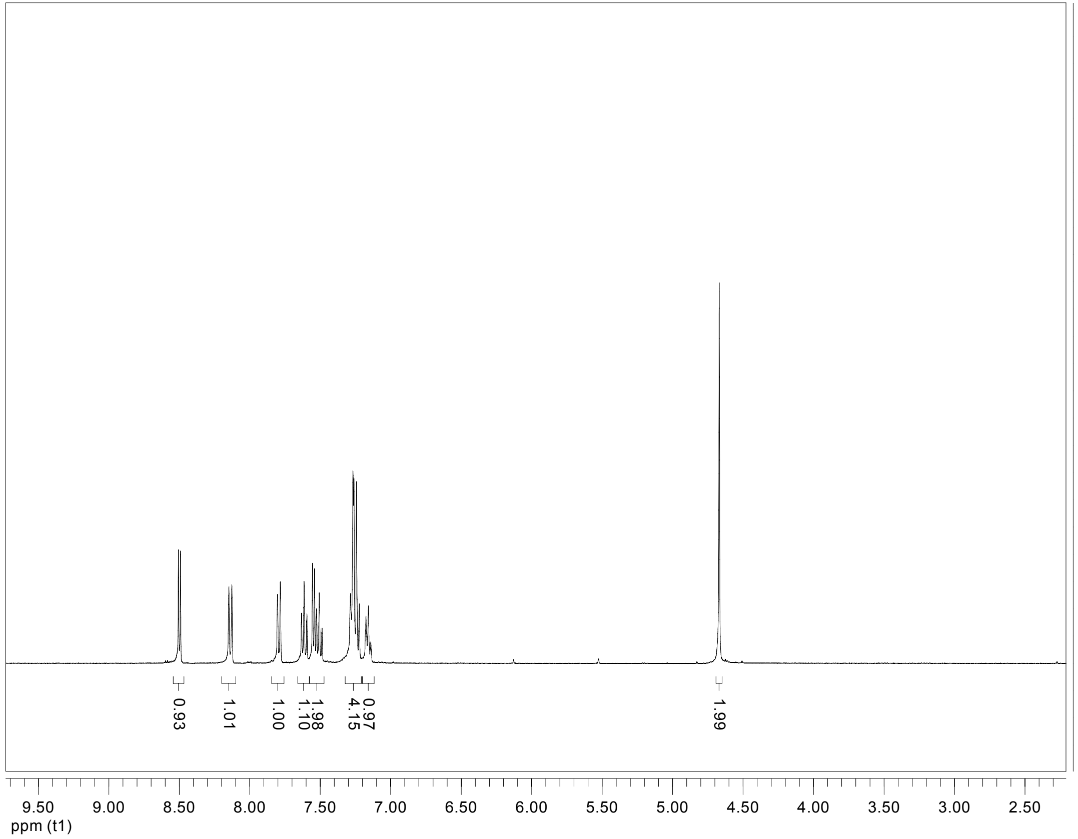
ppm (t1)


Br
N
CN
O

2k



^{1}H and ^{13}C NMR Spectra of Isoquinolines 3a-f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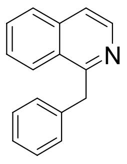
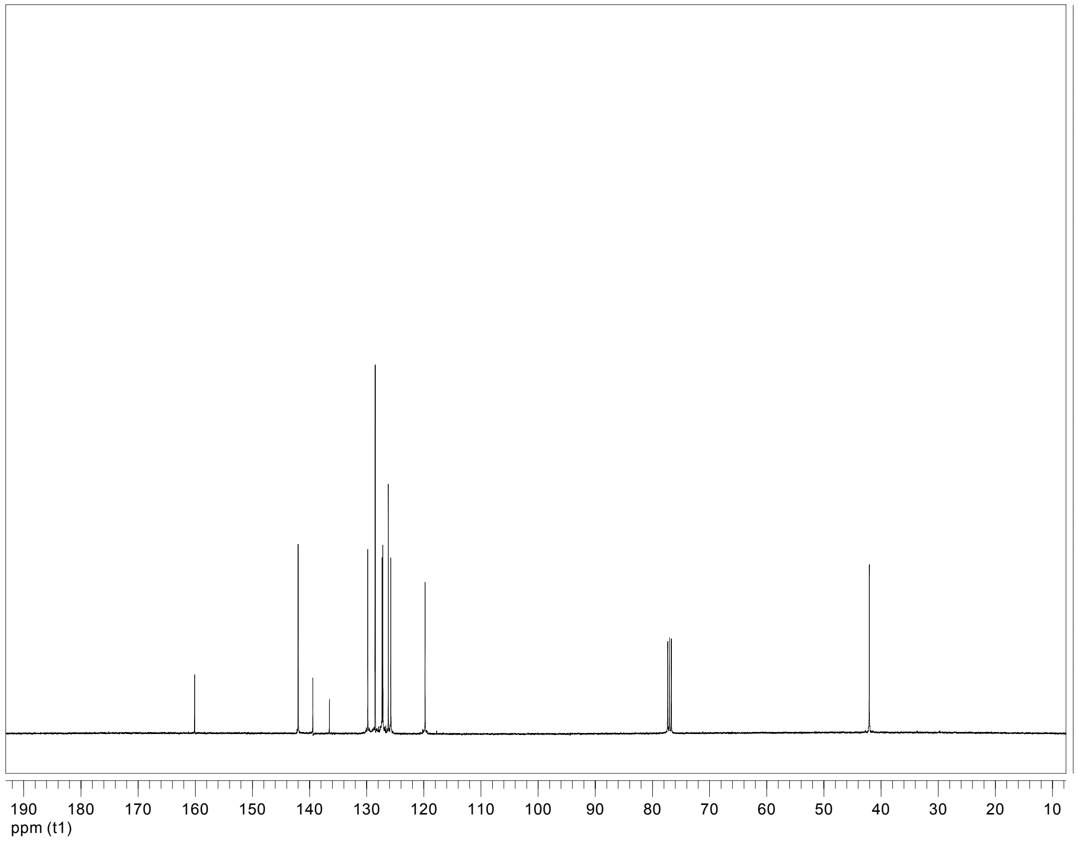
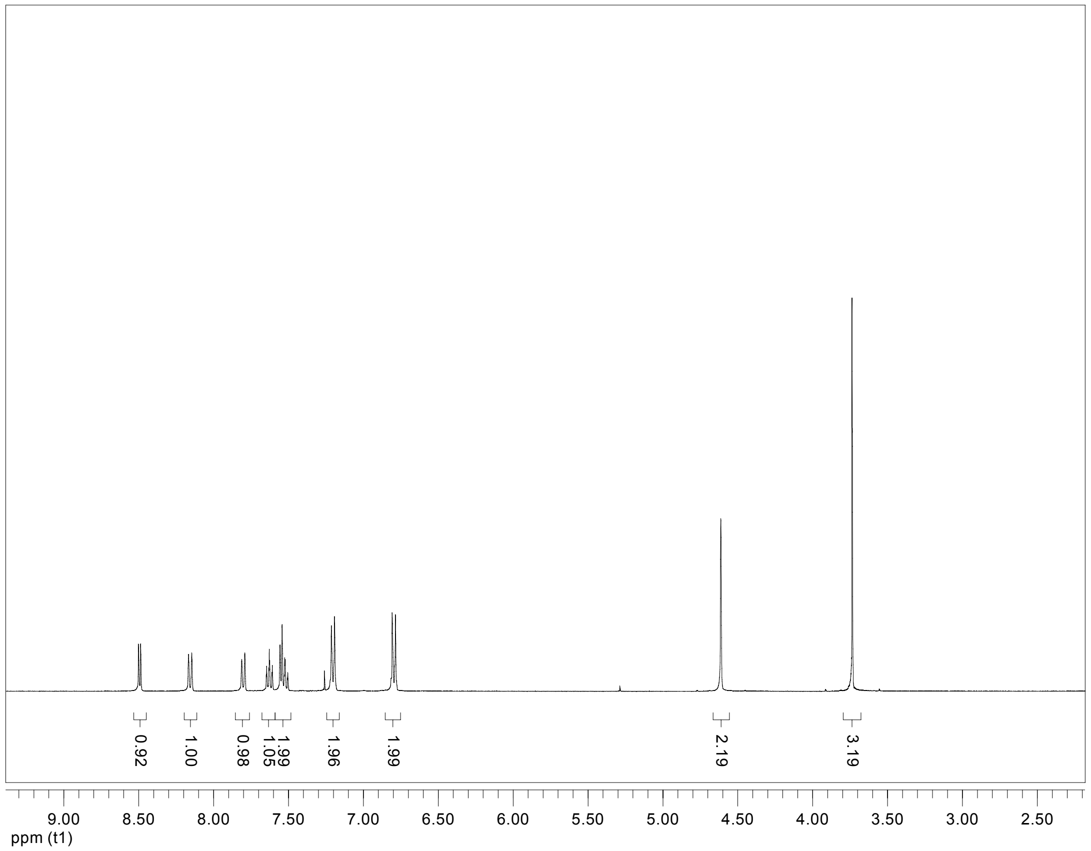
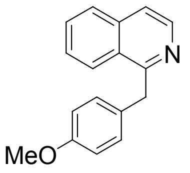
1.01
1.00
1.10
1.98
4.15
0.97
1.99
9.50
9.00
8.50
8.00
7.50
7.00
6.50
6.00
5.50
5.00
4.50
4.00
3.50
3.00
2.50
ppm (t1)


N

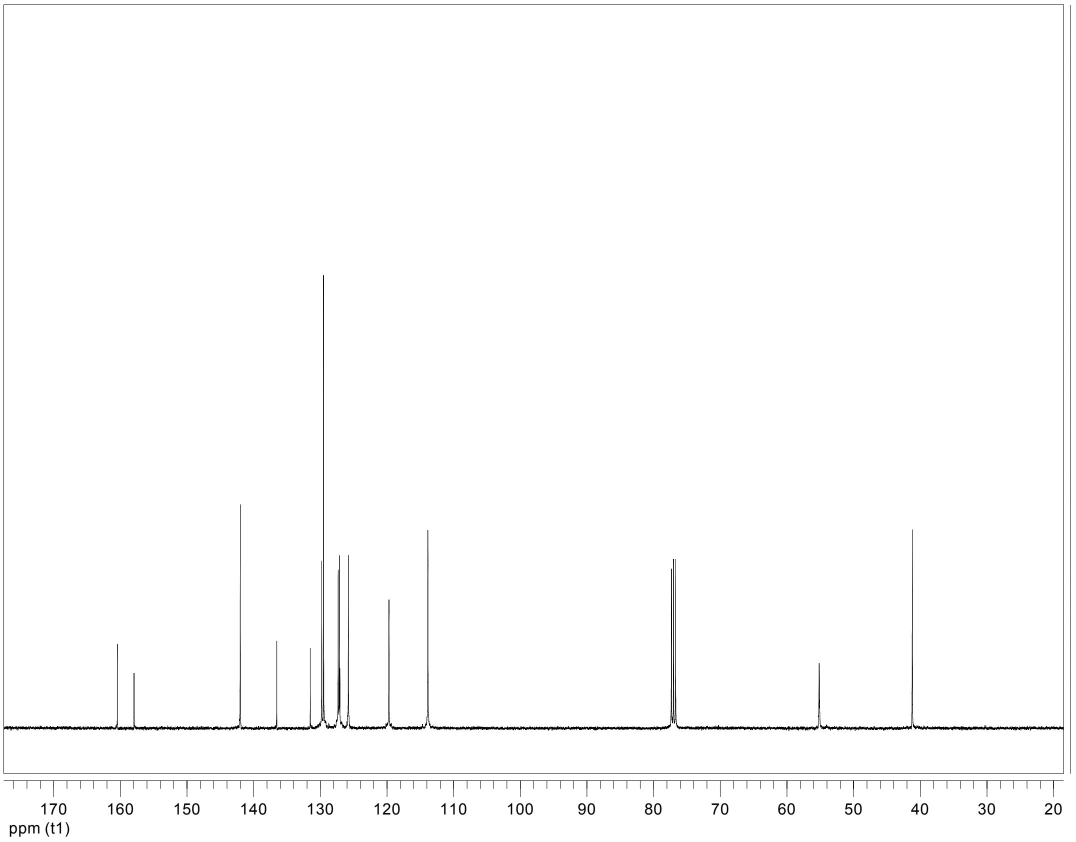
3a


190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm (t1)


0.92
1.00
0.98
1.05
1.99
1.96
1.99
2.19
3.19
9.00
8.50
8.00
7.50
7.00
6.50
6.00
5.50
5.00
4.50
4.00
3.50
3.00
2.50
ppm (t1)


N
MeO

3b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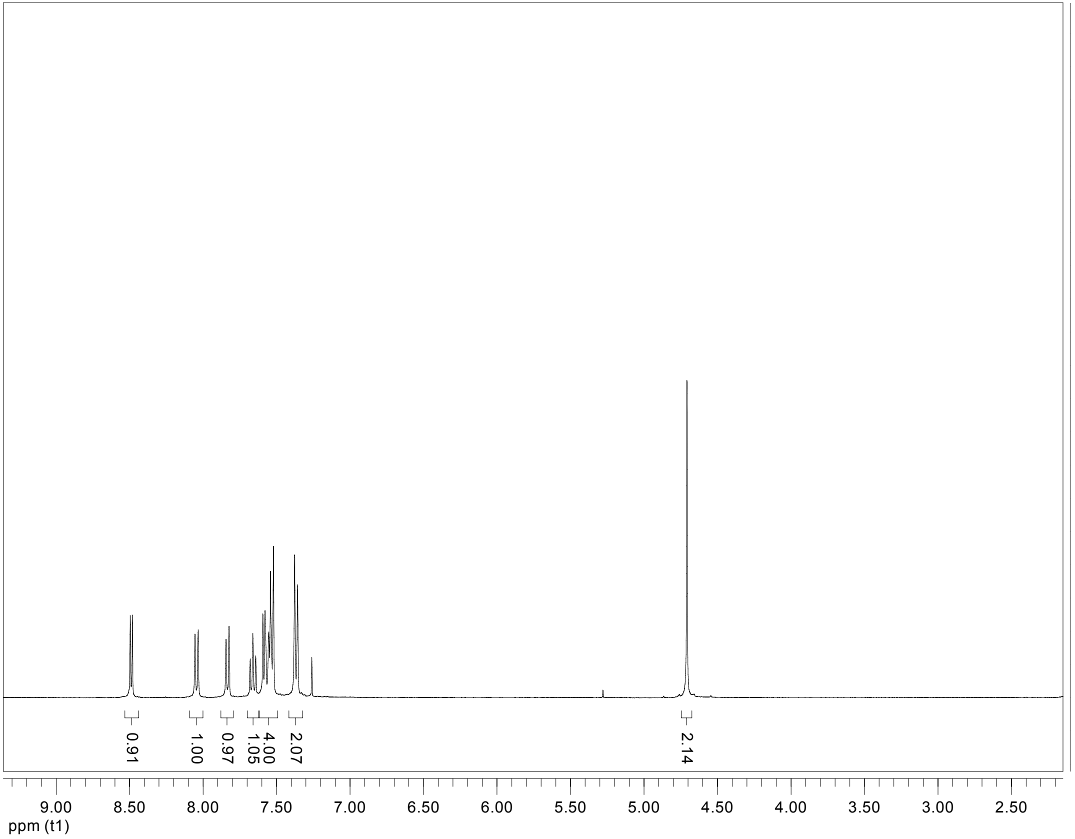
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm (t1)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2.07
2.14
9.00
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8.00
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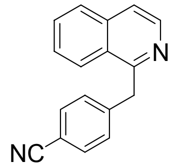
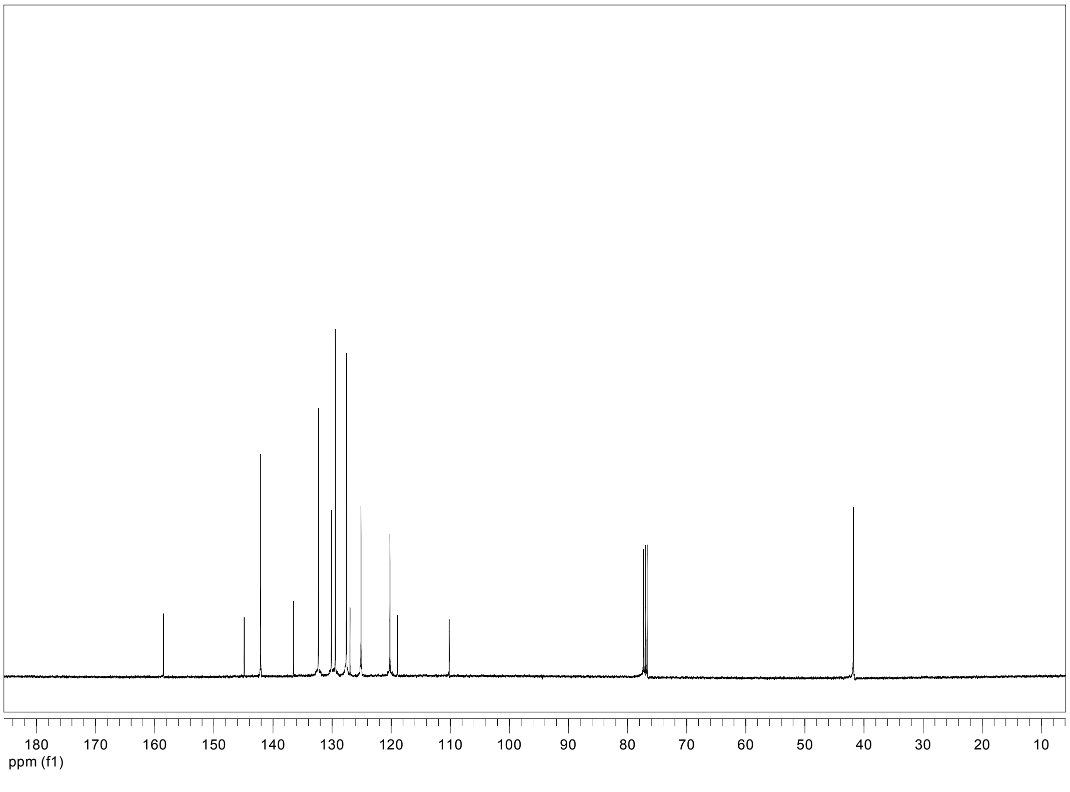
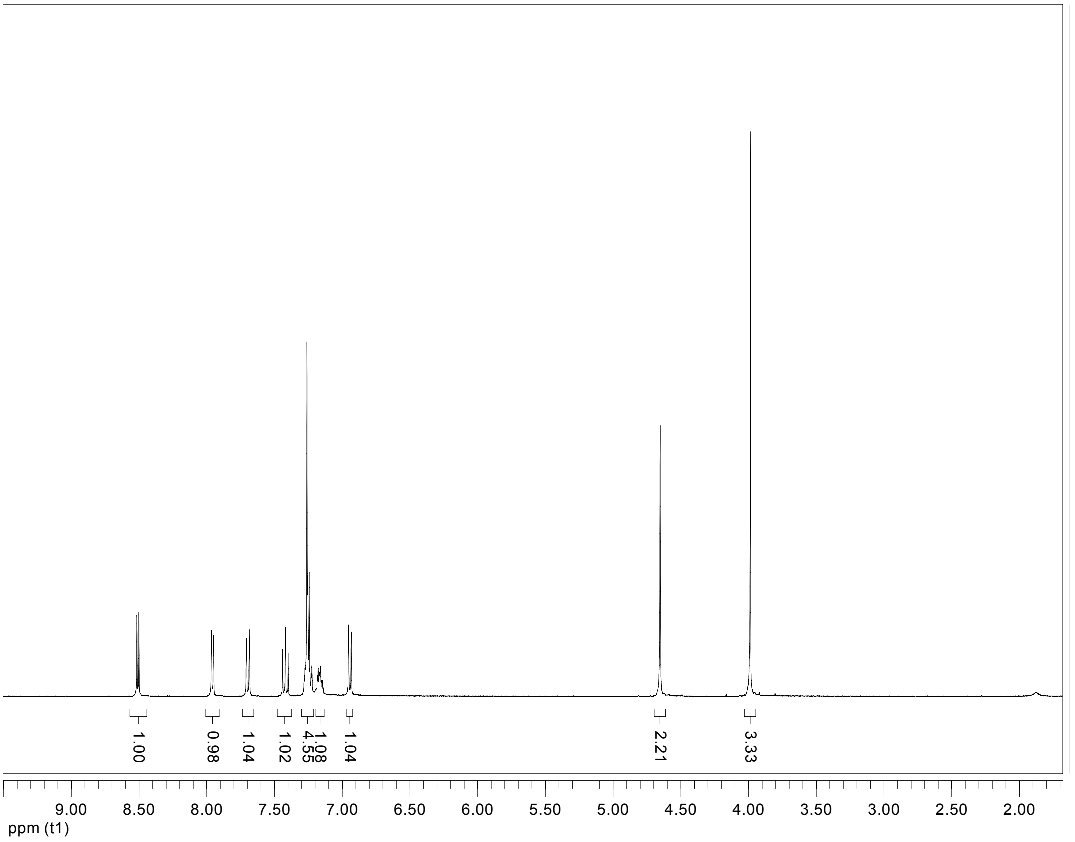
7.00
6.50
6.00
5.50
5.00
4.50
4.00
3.50
3.00
2.50
ppm (t1)


N
NC

3c


180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm (f1)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1.04
1.02
4.55
1.08
1.04
2.21
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9.00
8.50
8.00
7.50
7.00
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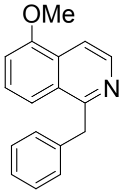
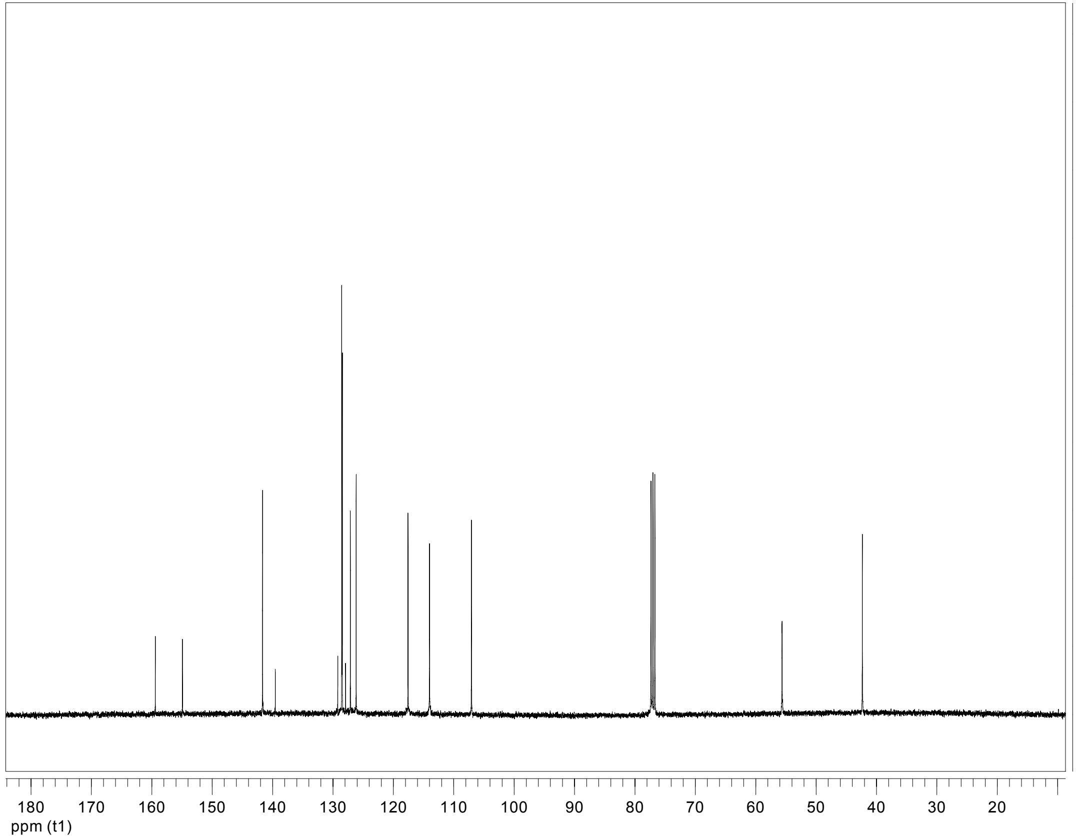
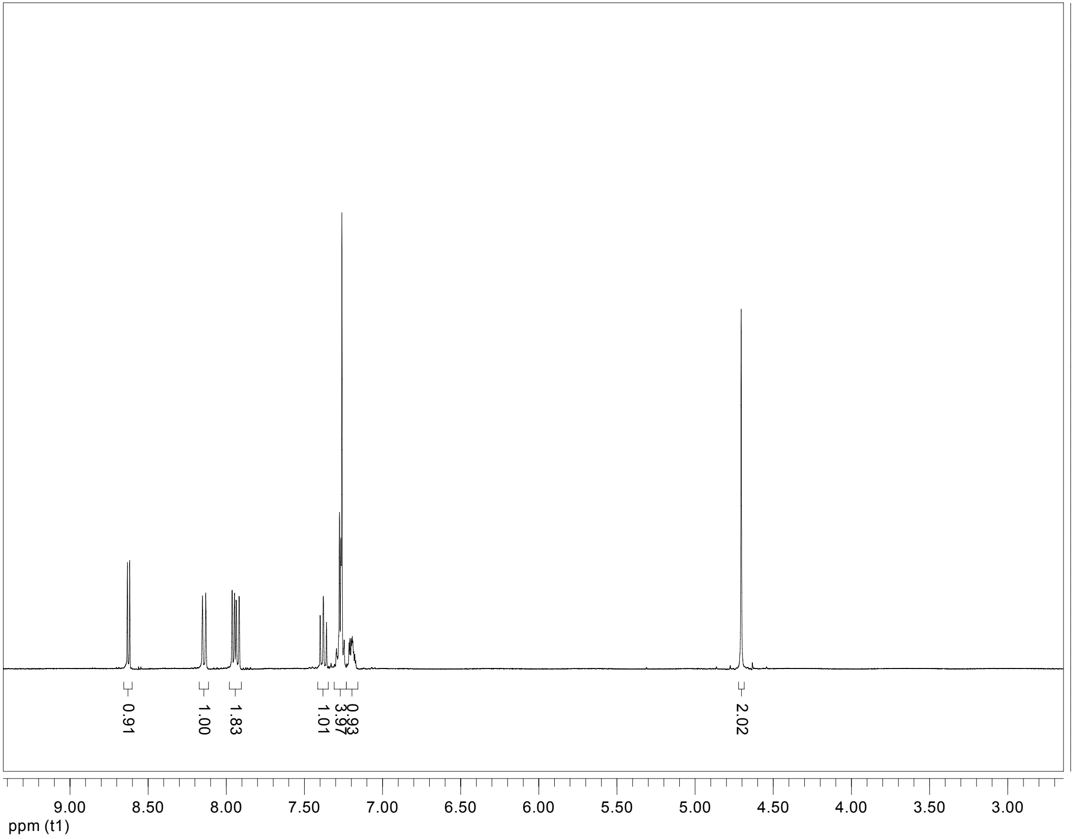
6.00
5.50
5.00
4.50
4.00
3.50
3.00
2.50
2.00
ppm (t1)


OMe
N

3d


180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm (t1)


0.91
1.00
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1.01
3.97
0.93
2.02
9.00
8.50
8.00
7.50
7.00
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5.00
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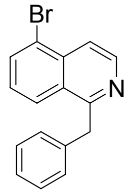
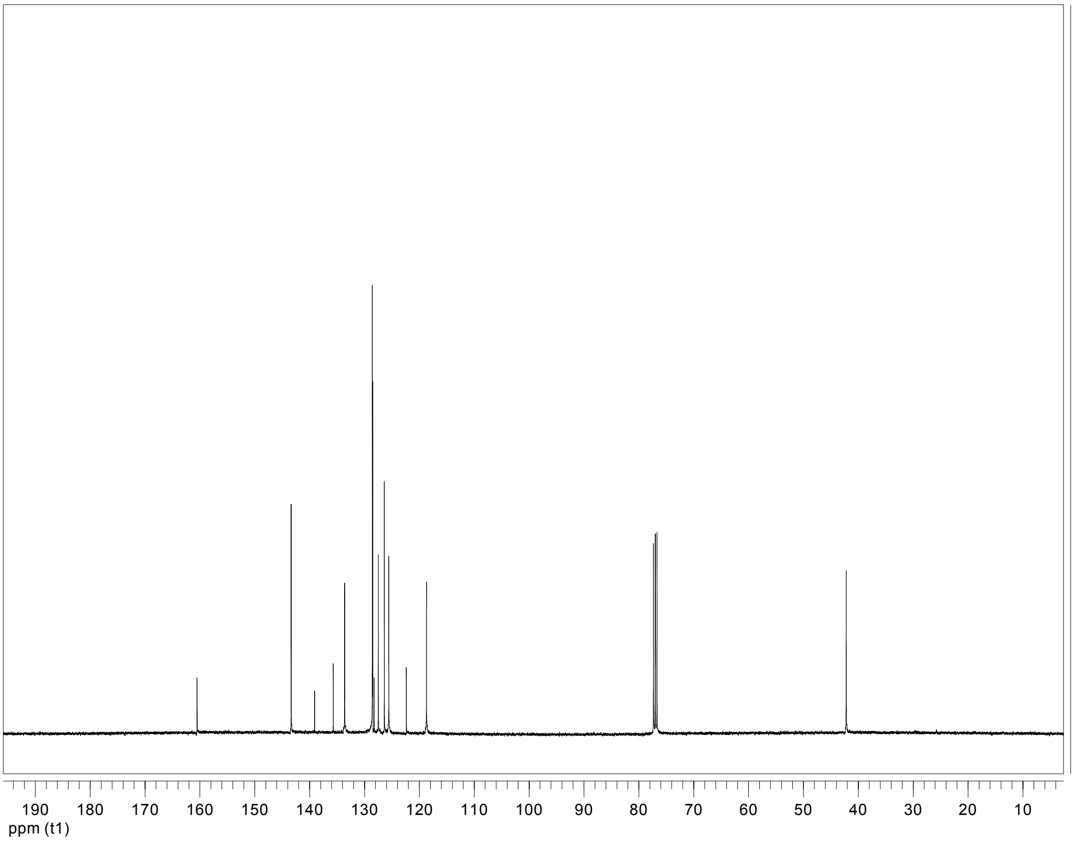
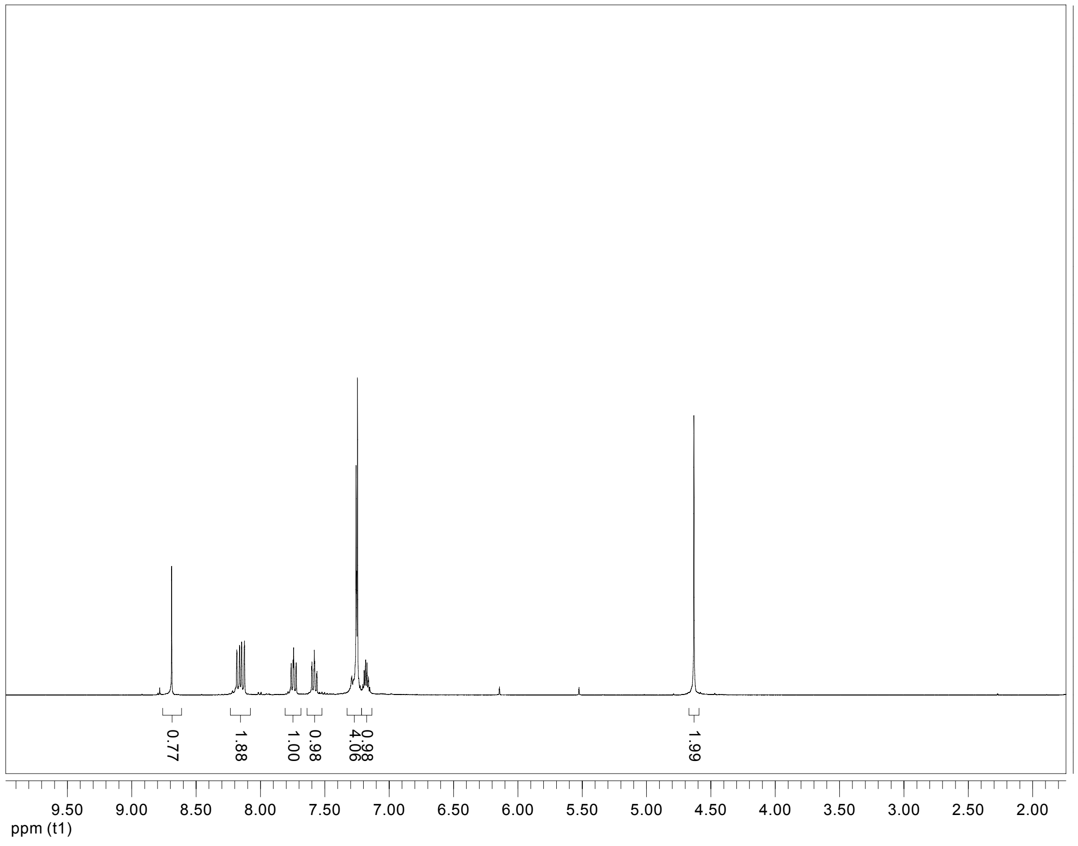
4.00
3.50
3.00
ppm (t1)


Br
N

3e


190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm (t1)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0.98
4.06
0.98
1.99
9.50
9.00
8.50
8.00
7.50
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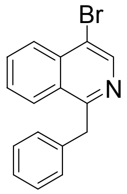
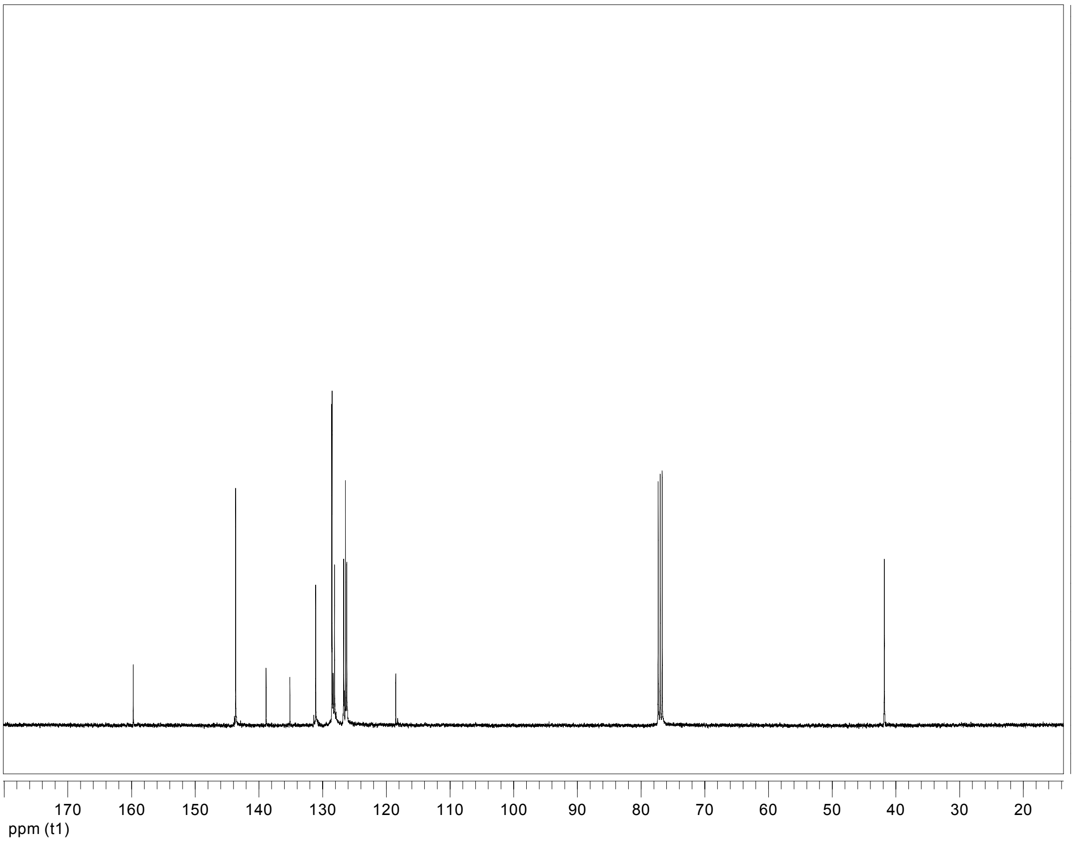
3.00
2.50
2.00
ppm (t1)


Br
N

3f



References

1. See also: D. G. Blackmond, *J. Am. Chem. Soc.*, **2001**, *123*, 545.
2. For more details see: H. B. Kagan and J. C. Fiaud, in *Topics in Stereochemistry*, ed. E. L. Eliel and S. H. Wilen, Interscience, New York, 1988, vol. 18, p. 249.