

Reductive Conjugate Addition nitro-Mannich Route for the Stereoselective Synthesis of 1,2,3,4-Tetrahydroquinoxalines

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Supplementary Information

General experimental

X-ray structure

p*K*_a measurements

Copies of ¹H and ¹³C NMR spectra:

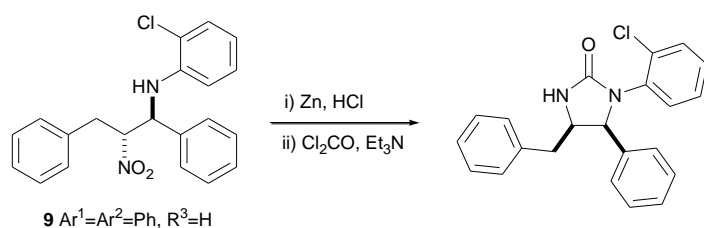
General experimental. Unless otherwise stated, all reactions were carried out under an atmosphere of nitrogen. All glassware was flame/heat gun dried and allowed to cool under a stream of nitrogen before use. Cooling to 0 °C was effected using an ice-water bath. Cooling to temperatures below 0 °C was effected using dry ice-acetone mixtures. Infra-red spectra were recorded on Perkin Elmer Spectrum One FT-IR spectrometers, with absorption reported in wavenumbers (cm⁻¹). Proton magnetic resonance spectra (¹H NMR) were recorded at 400 or 600 MHz on Bruker Avance 400 or 600 spectrometers respectively. Carbon magnetic resonance spectra (¹³C NMR) were recorded at 101 or 151 MHz on Bruker Avance 400 or 600 spectrometers respectively. If not specifically stated, the NMR experiments were run at 20 °C. Chemical shifts (δ) are quoted in parts per million (ppm) and referenced to the residual solvent peak. Coupling constants (*J*) are quoted in Hertz (Hz). High resolution mass spectra (HRMS) were collected on a Thermo Finnigan Mat900xp (EI/CI) VG-70se (FAB) and Waters LCT Premier XE (ES) instruments. Reactions were monitored by thin layer chromatography (TLC) using Polygram[®] SIL G/UV254 0.25 mm silica gel precoated plastic plates with fluorescent indicator. Sheets were visualised using ultra-violet light (254 nm) and/or KMnO₄ solutions, as appropriate. Liquid chromatography was by automation using the Flashmaster II available from Argonaut Technologies Ltd, which utilises disposable, normal phase, pre-packed

cartridges SPE cartridges. SPE (solid phase extraction) refers to the use of cartridges sold by International Sorbent Technology Ltd. It provides quaternary on-line solvent mixing to enable gradient methods to be run. Samples are queued using the multi-functional open access software, which manages solvents, flow-rates, gradient profile, and collection conditions. The system is equipped with a Knauer variable wavelength UV-detector and two Gilson FC204 fraction-collectors enabling automated peak cutting, collection and tracking. Melting points were recorded on Stuart Automatic Melting Point, SMP40.

Nitroalkenes¹ and imines² were prepared according to literature procedures.

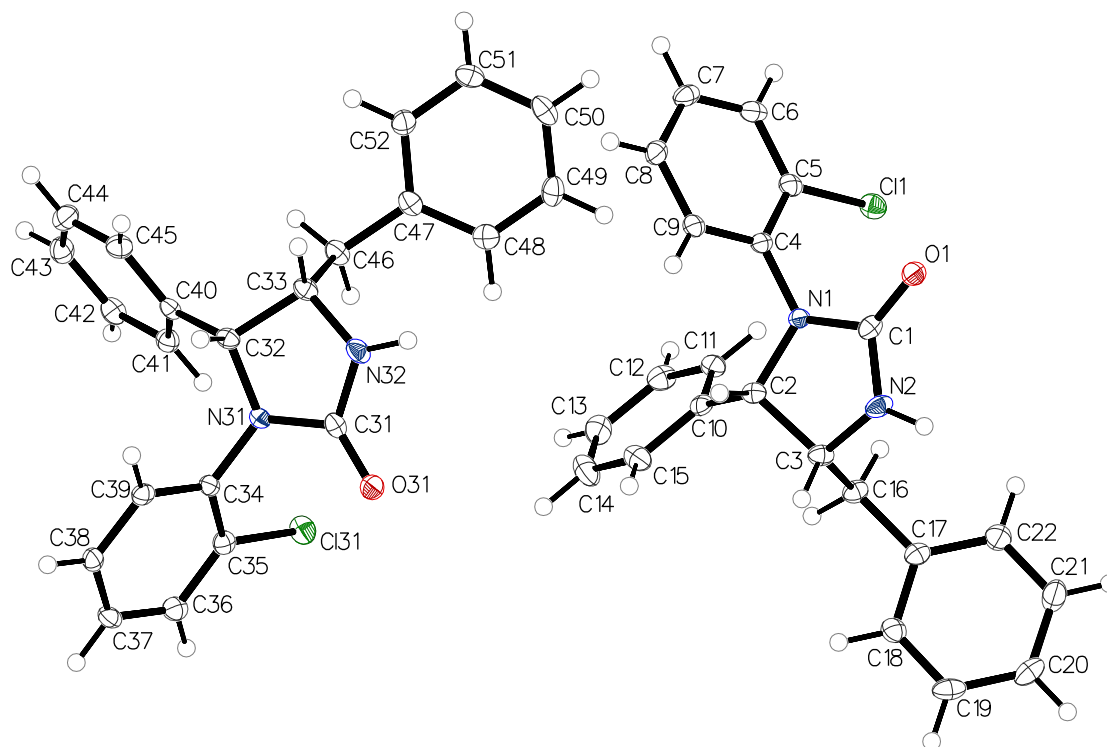
X-ray structure of derivative of **9b**.

Reduction of β -nitroamine **9b** was carried out with Zn/HCl as detailed in the paper and the crude product treated with phosgene according to our previous procedure.³



Data for (**4R***, **5S***)-4-benzyl-1-(2-chlorophenyl)-5-phenylimidazolidin-2-one

White solid, mp 150-152 °C; ¹H NMR (500 MHz; CDCl₃) δ 2.35 (1H, dd, J =13.9, 9.9), 2.40 (1H, dd, J =13.9, 4.3), 4.40 (1H, app. dddd, J =9.9, 8.5, 4.3, 1.1), 4.61 (1H, br.s), 5.49 (1H, d, J =8.8), 7.04-7.16 (4H, m), 7.19-7.42 (10H, m); ¹³C NMR (126 MHz; CDCl₃) δ 38.2, 47.7, 56.8, 65.3, 127.0, 127.4, 128.4 (2C), 128.6, 128.7 (2C), 128.9 (2C), 129.0 (2C), 130.1, 130.5, 132.6, 135.0, 135.8, 137.6, 159.9; IR (neat) 3240, 3030, 2924, 1708, 1484 cm⁻¹; Mass Spec (ES, M + H) Theoretical: 363.1264, Measured: 363.1267.



Crystallographic data (excluding structure factors) for this structure has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 1491434. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

| | | |
|--|---|---------------------------|
| Formula weight | 362.84 | |
| Temperature | 100(2) K | |
| Wavelength | 0.71075 Å | |
| Crystal system | Monoclinic | |
| Space group | <i>P</i> 21/ <i>c</i> | |
| Unit cell dimensions | <i>a</i> = 18.6683(5) Å | $\alpha = 90^\circ$ |
| | <i>b</i> = 10.1255(2) Å | $\beta = 93.979(7)^\circ$ |
| | <i>c</i> = 18.9205(13) Å | $\gamma = 90^\circ$ |
| Volume | 3567.8(3) Å ³ | |
| <i>Z</i> | 8 | |
| Density (calculated) | 1.351 Mg / m ³ | |
| Absorption coefficient | 0.227 mm ⁻¹ | |
| <i>F</i> (000) | 1520 | |
| Crystal | Block; Colourless | |
| Crystal size | 0.10 × 0.07 × 0.05 mm ³ | |
| θ range for data collection | 3.09 – 27.48° | |
| Index ranges | –24 ≤ <i>h</i> ≤ 24, –12 ≤ <i>k</i> ≤ 12, –24 ≤ <i>l</i> ≤ 23 | |
| Reflections collected | 24168 | |
| Independent reflections | 8114 [<i>R</i> _{int} = 0.0267] | |
| Completeness to $\theta = 27.48^\circ$ | 99.2 % | |

| | |
|--|---|
| Absorption correction | Semi-empirical from equivalents |
| Max. and min. transmission | 0.9887 and 0.9776 |
| Refinement method | Full-matrix least-squares on F^2 |
| Data / restraints / parameters | 8114 / 2 / 475 |
| Goodness-of-fit on F^2 | 1.035 |
| Final R indices [$F^2 > 2\sigma(F^2)$] | $R1 = 0.0386$, $wR2 = 0.0866$ |
| R indices (all data) | $R1 = 0.0522$, $wR2 = 0.0924$ |
| Largest diff. peak and hole | 0.318 and $-0.277 \text{ e } \text{\AA}^{-3}$ |

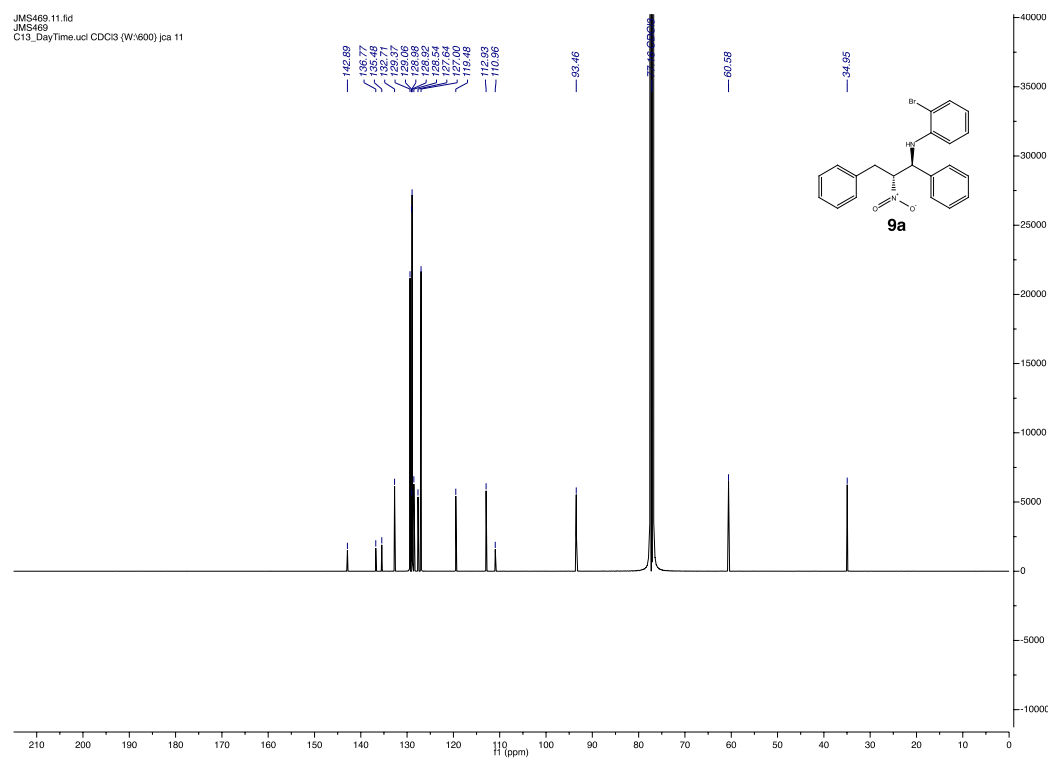
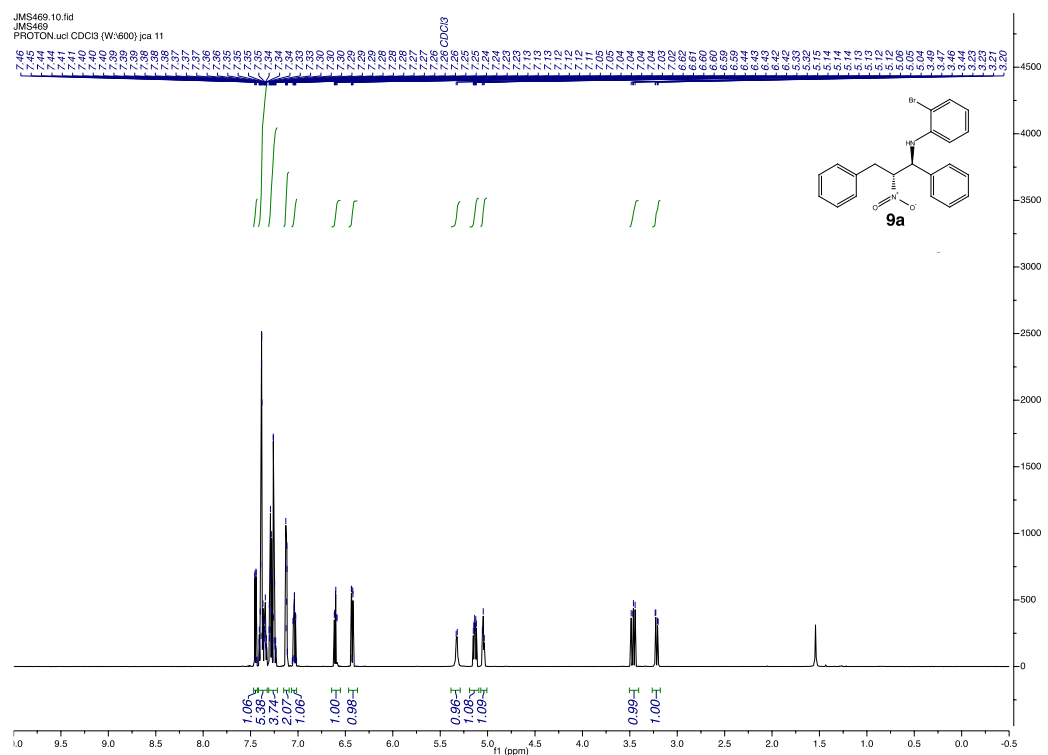
p*K*_a measurements

A Sirius T3 (Sirius Analytical Inc, UK) instrument was used for p*K*_a determination of compounds. The p*K*_a determination was based on acid-base titration and the protonation/deprotonation of the molecule was measured either by UV spectroscopy. The p*K*_a value was calculated from the pH where the 50-50% of the protonated and unprotonated form of the molecules are present. The UV-metric method provides p*K*_a results for samples with chromophores whose UV absorbance changes as a function of pH. It typically required 5 μl of a 10 mM DMSO solution of the samples and the UV absorbance was monitored over the pH range 2-12 in a buffered solution in about 12 min. Usually 0.5-1 mg of solid material was required for the measurements. If the compound precipitated under the aqueous conditions, MeOH co-solvent was added using various concentrations, generally 50,40,30%. The p*K*_a in water was calculated using the Yasuda-Shedlovsky extrapolation method.^{4,5}

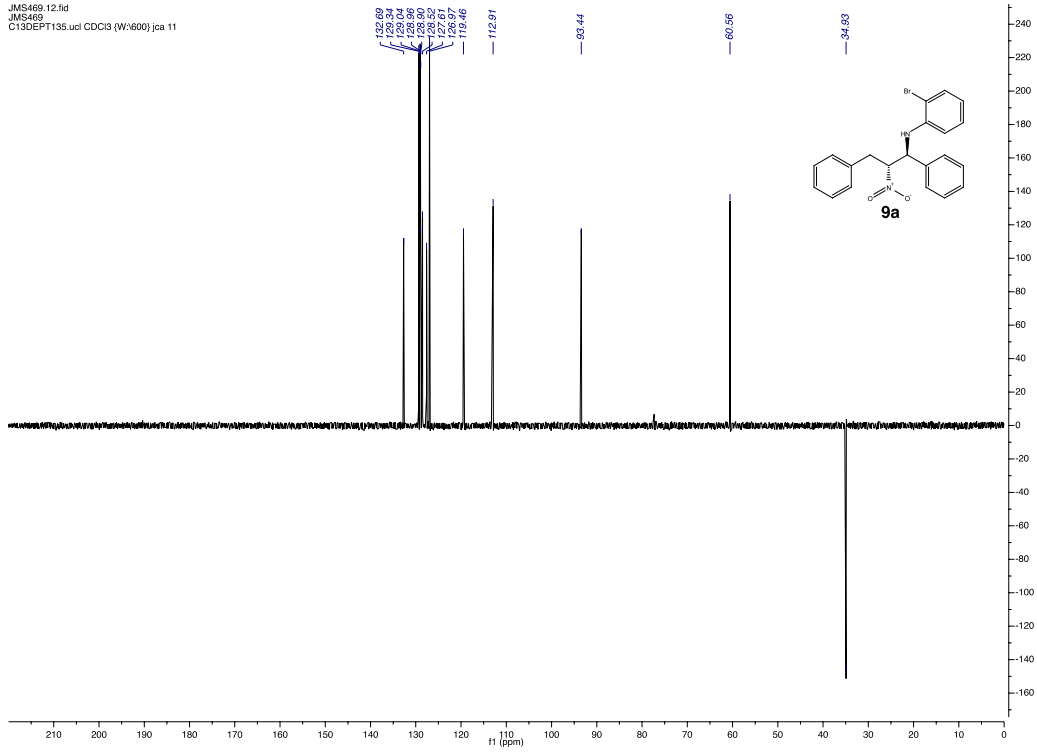
References

1. (a) L. F. Fieser and M. Gates, *J. Am. Chem. Soc.*, 1946, **68**, 2249. (b) J. Melton and J. E. McMurry, *J. Org. Chem.*, 1975, **40**, 2138. (c) G. Kumaran and G. H. Kulkarni, *Synthesis*, 1995, 1545. (d) D. Enders and J. Wiedemann, *Synthesis*, 1996, 1443.
2. J.C. Anderson, G. P. Howell, R. M. Lawrence and C. S. Wilson, *J. Org. Chem.*, 2005, **70**, 5665.
3. J.C. Anderson, A. J. Blake, P. J. Koovits, and G. J. Stepney, *J. Org. Chem.* 2012, **77**, 4711.
4. M. Yasuda, *Bull. Chem. Soc. Jpn.*, 1959, **32**, 429.
5. T. Shedlovsky in *Electrolytes*, B. Pesce Ed., Pergamon New York, 1962.

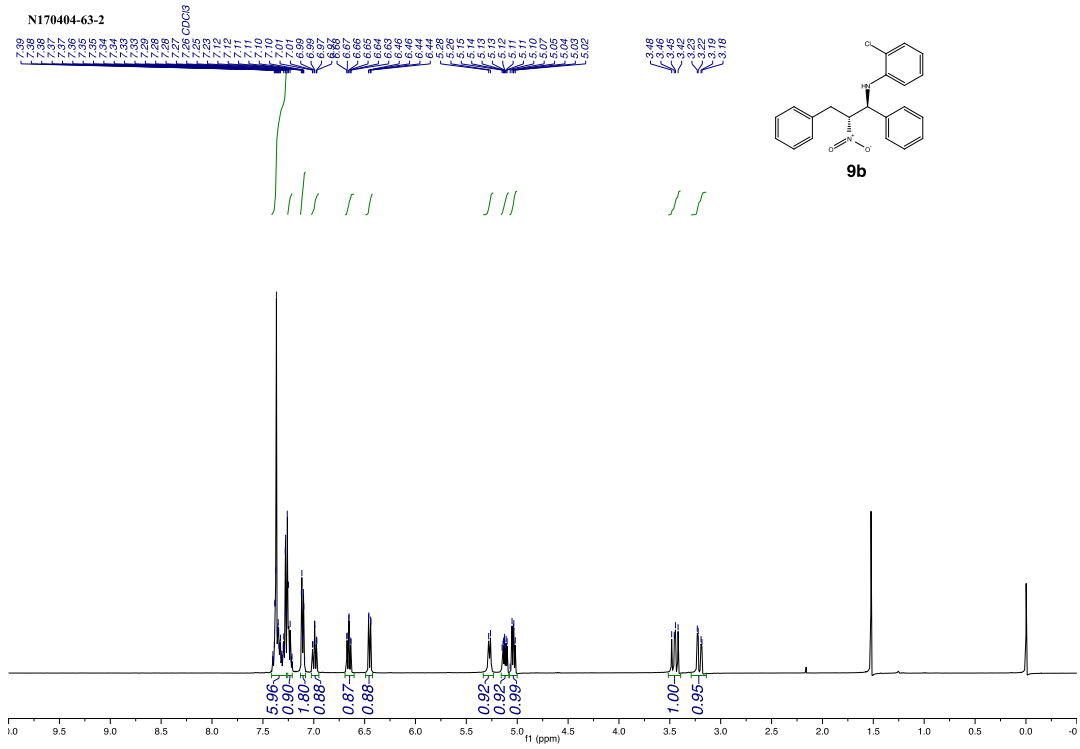
1H and 13C NMR Spectra



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 C13DEPT135.ucf CDCI3 (W/600) jca 11



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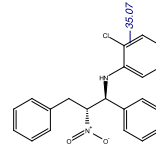


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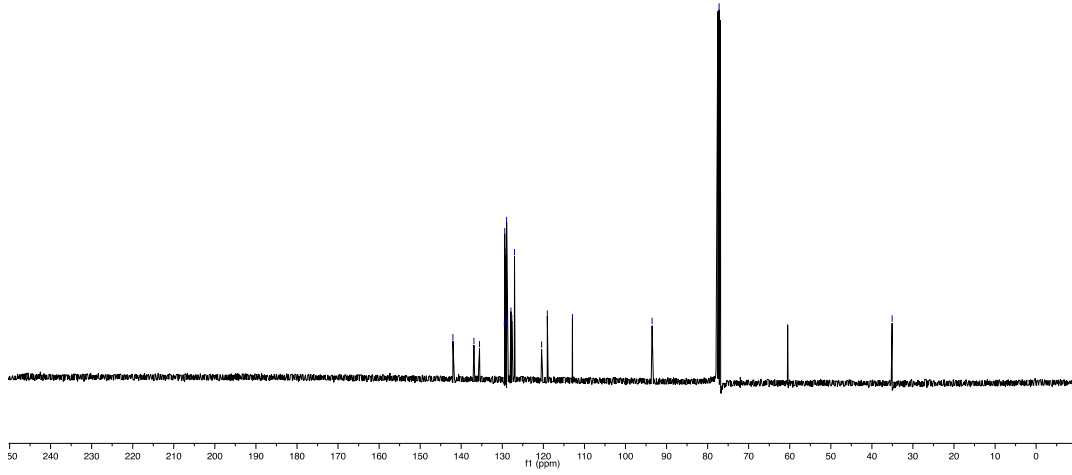
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138.92
138.41
133.50
133.02
129.65
127.68
127.03
119.03
112.93

83.54

77.20



9b



N170404-63-2

129.64

129.35

129.19

127.02

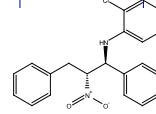
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113.15

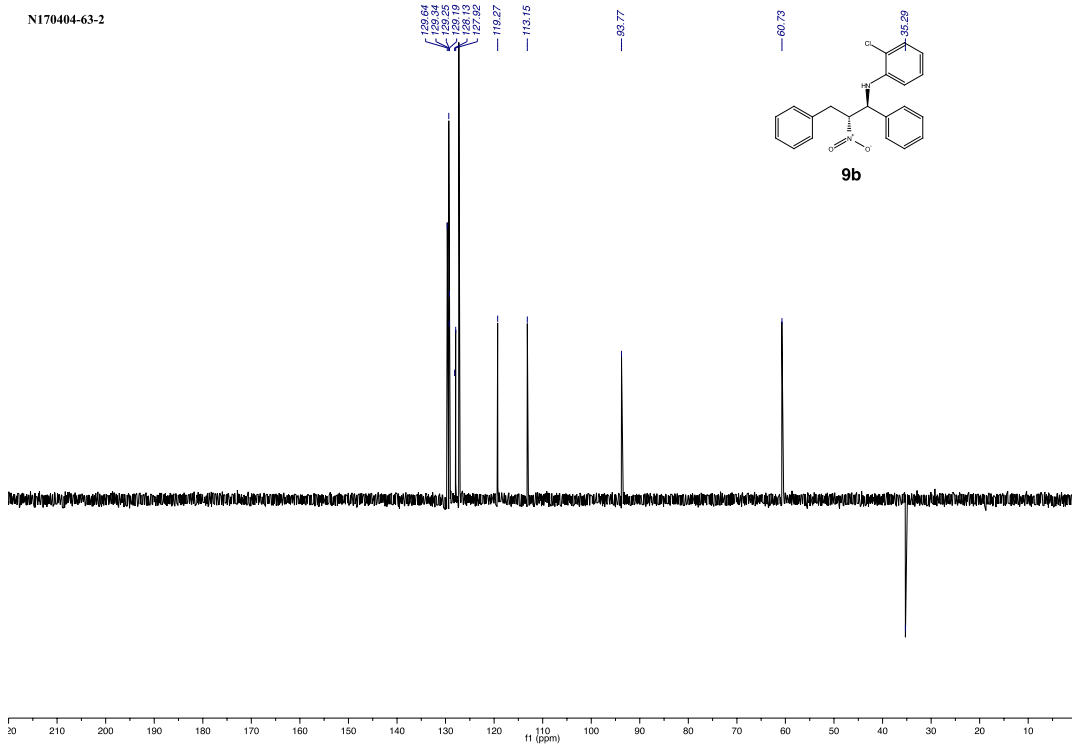
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60.73

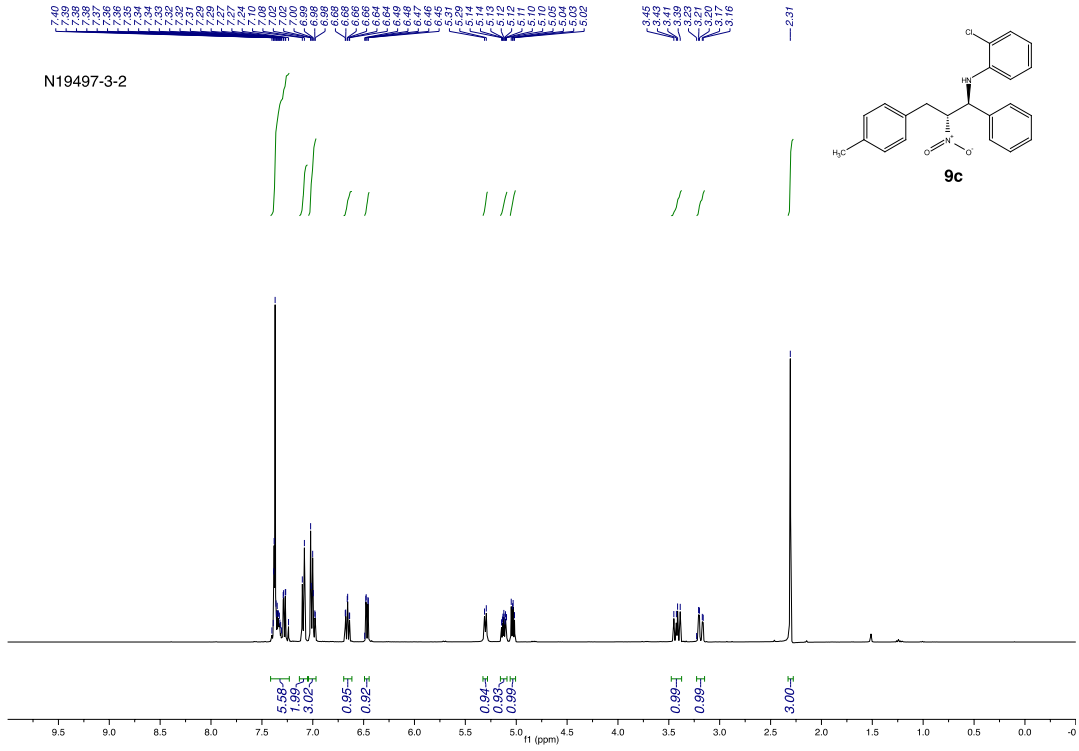
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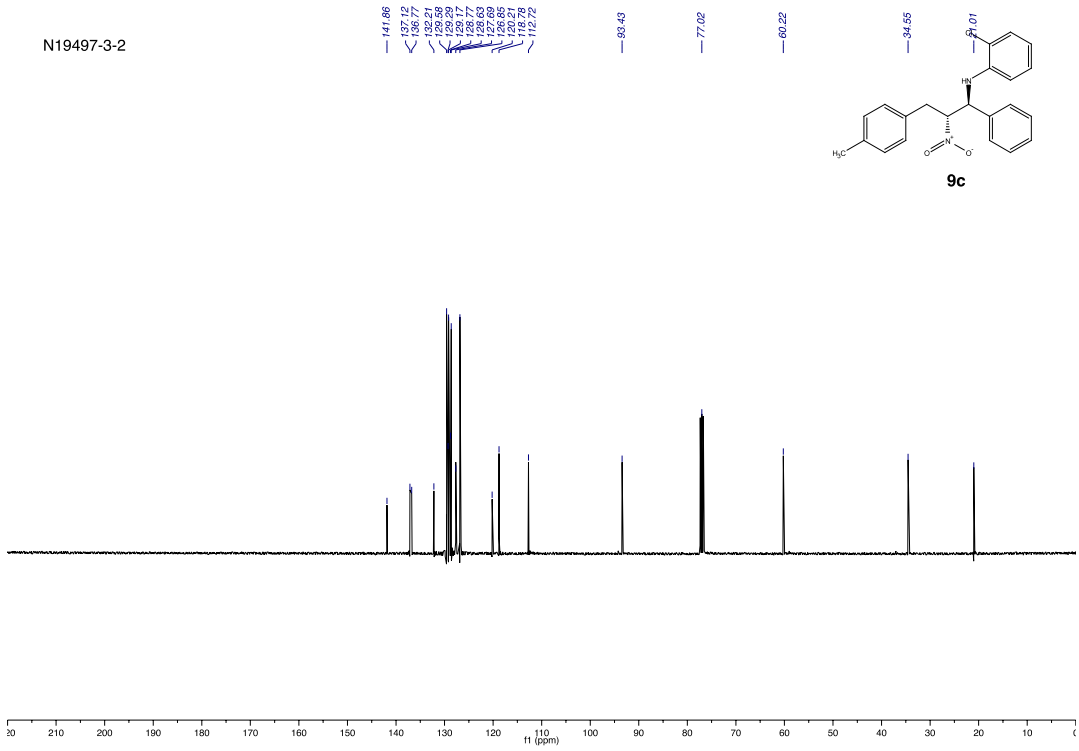
9b



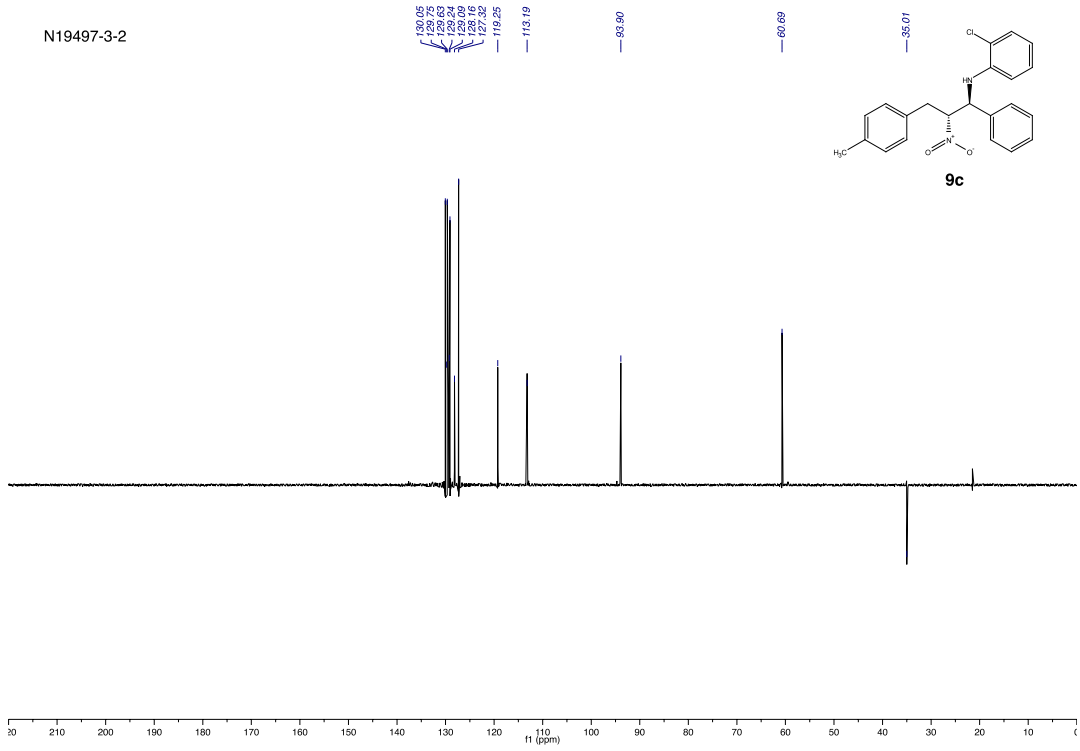
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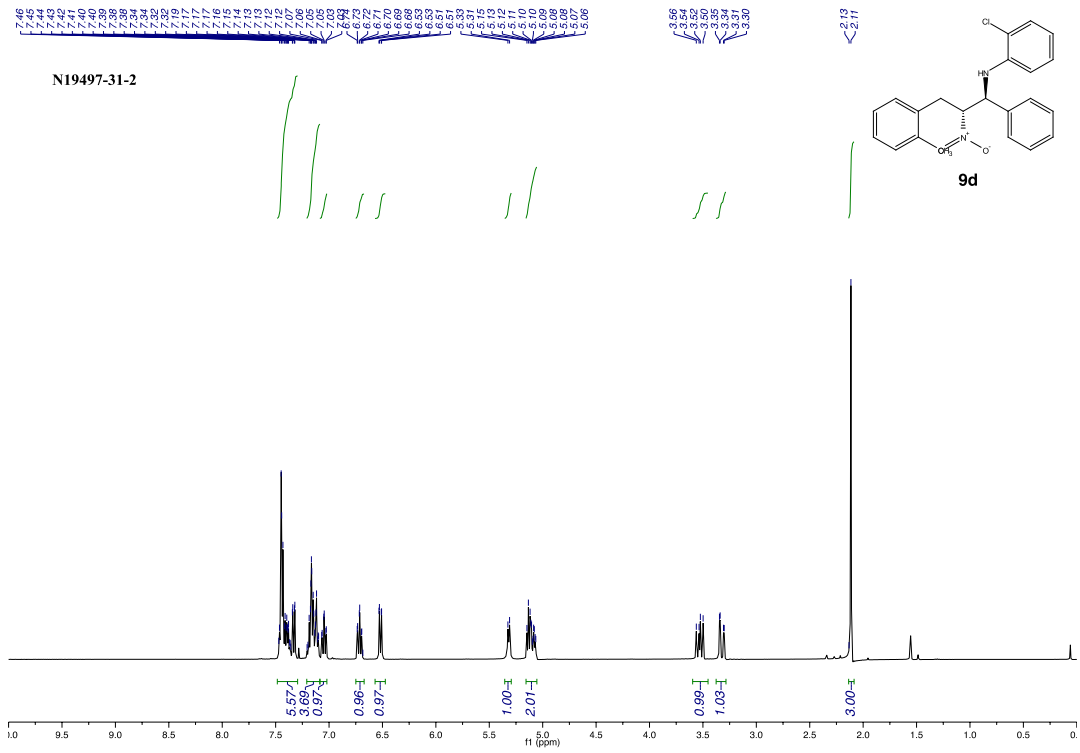
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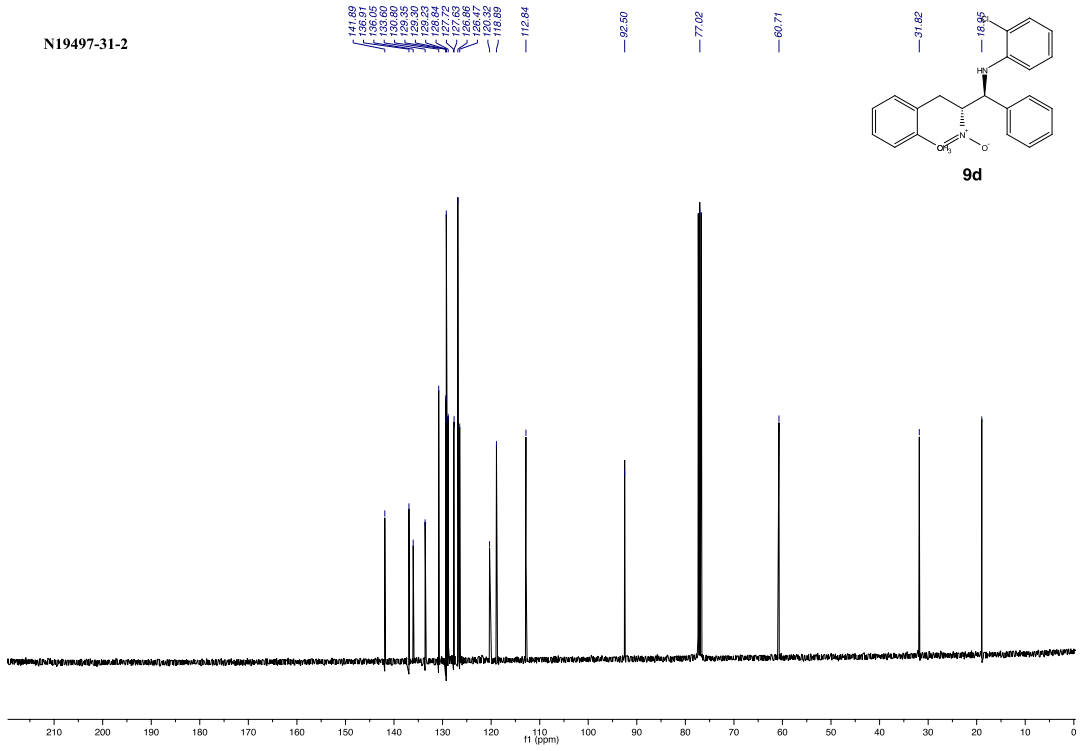
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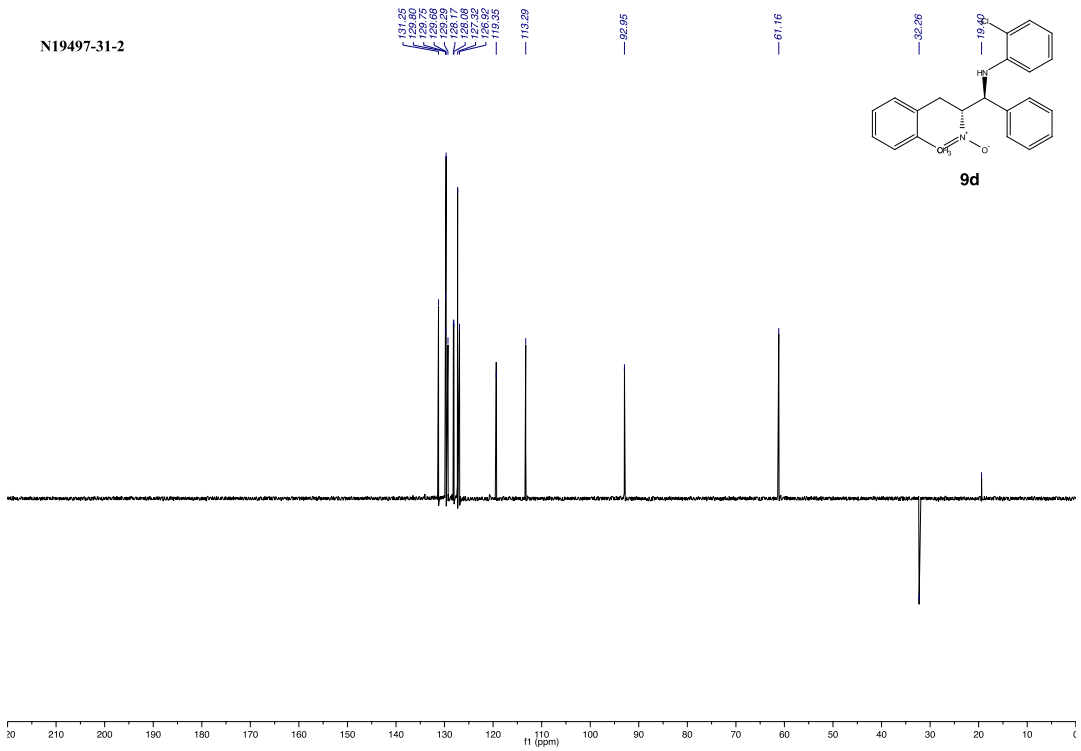
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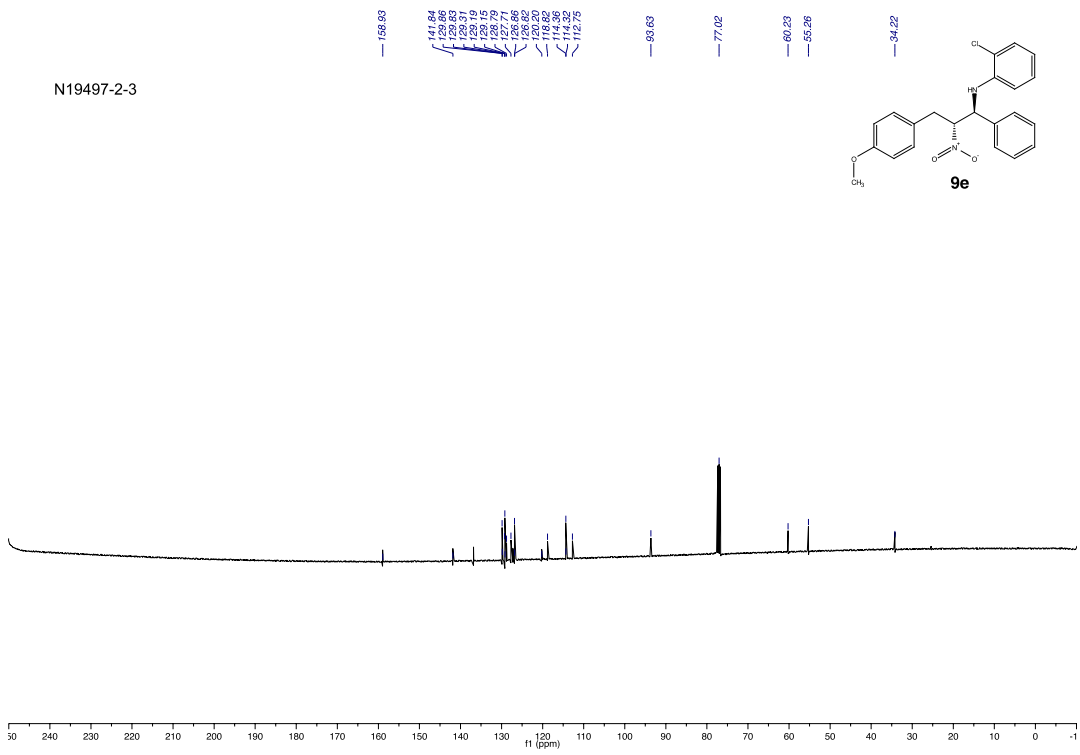
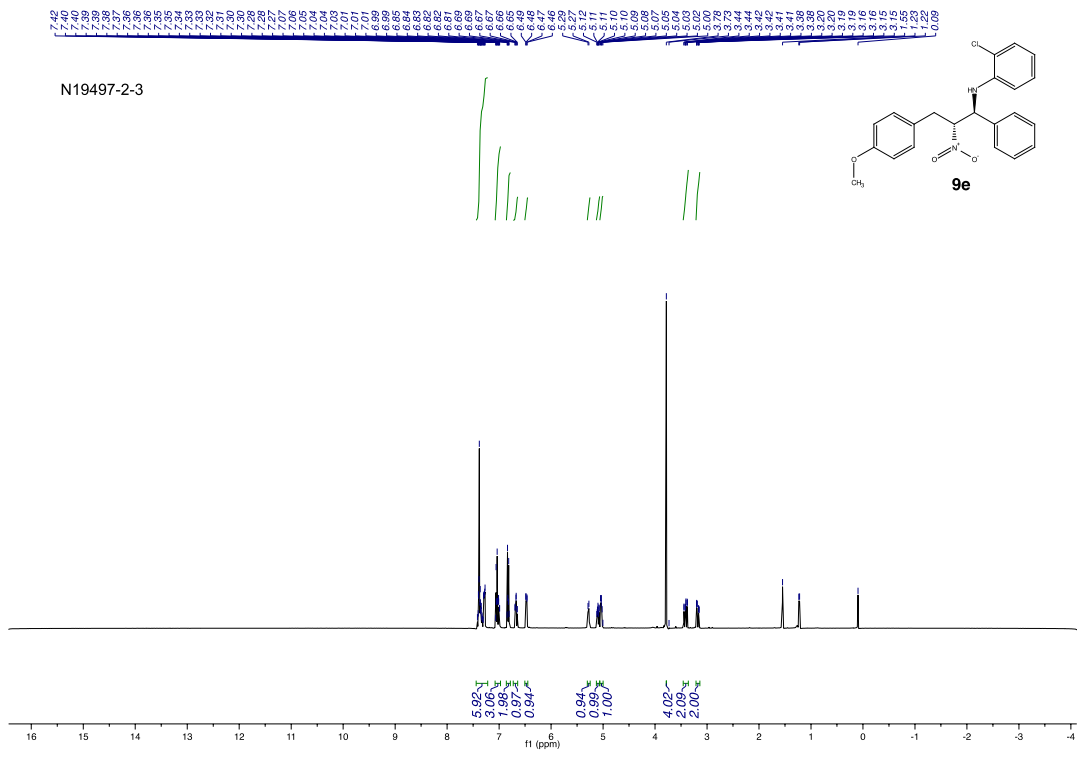


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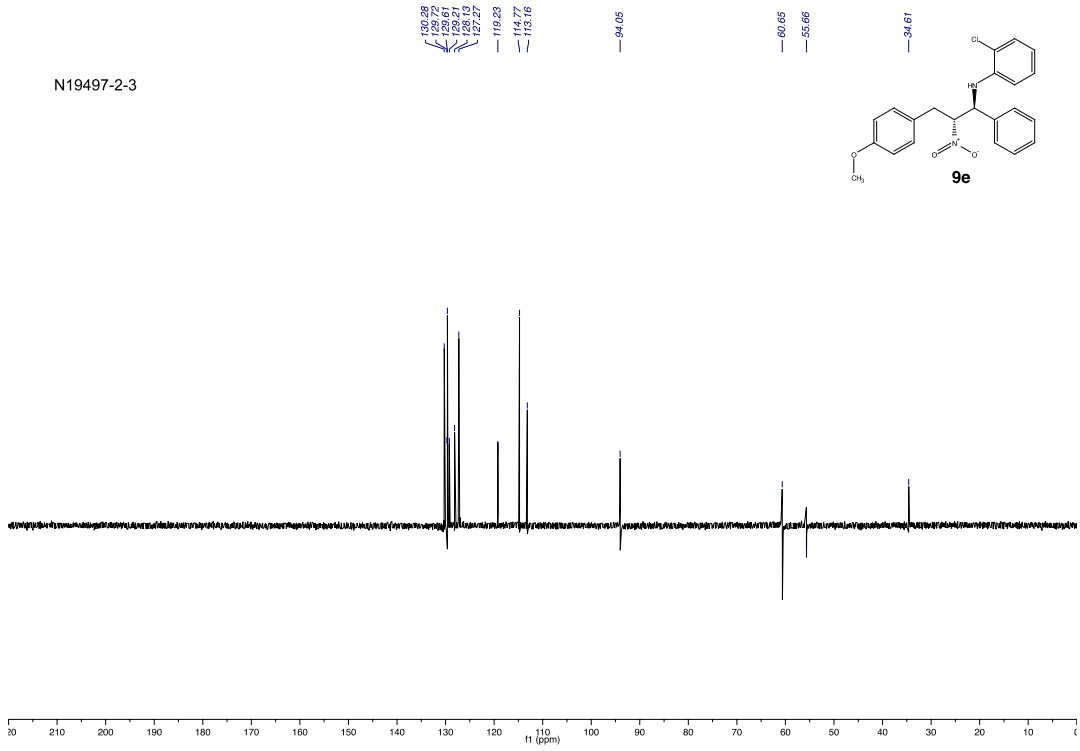


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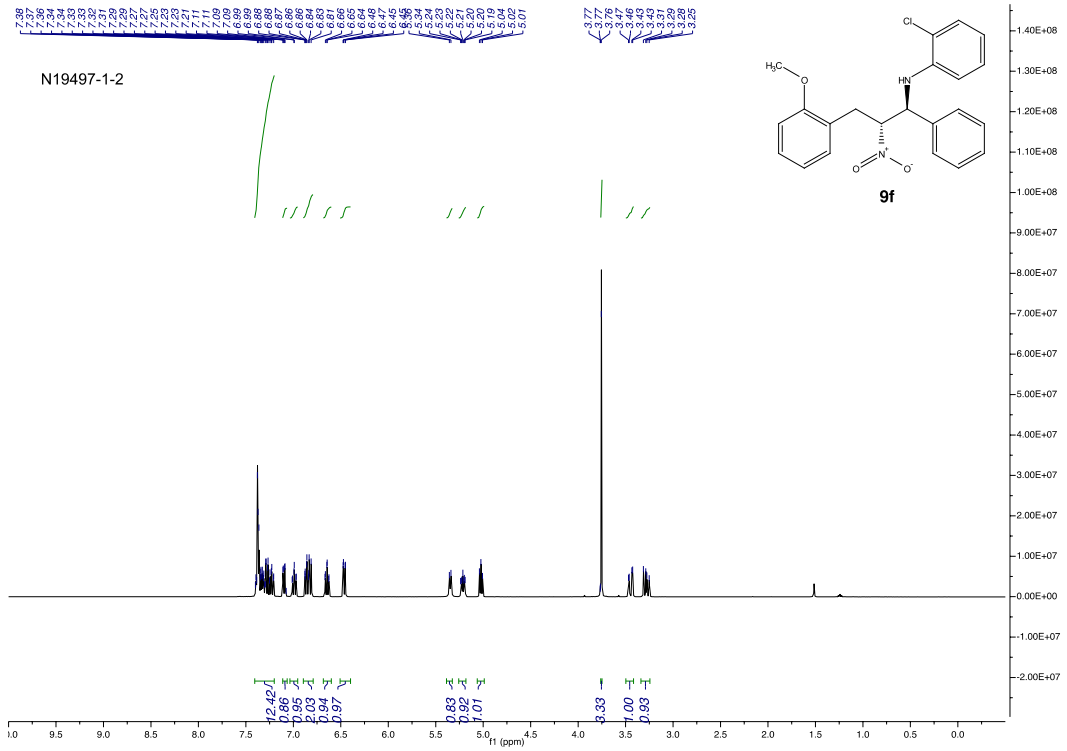




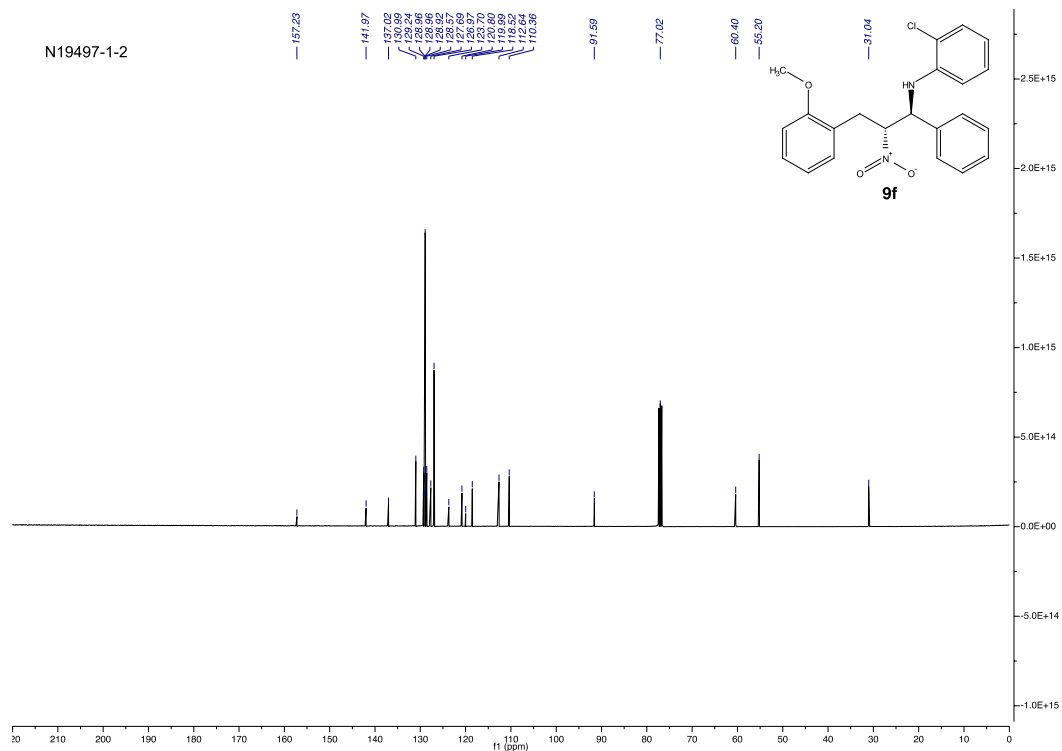
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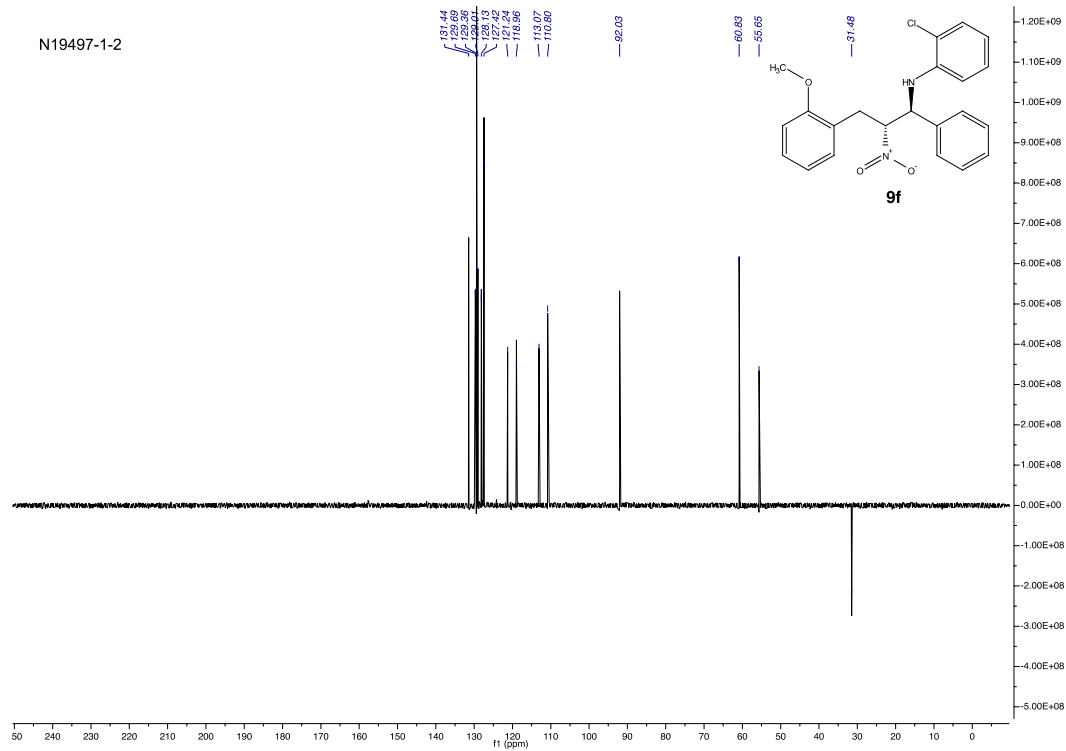
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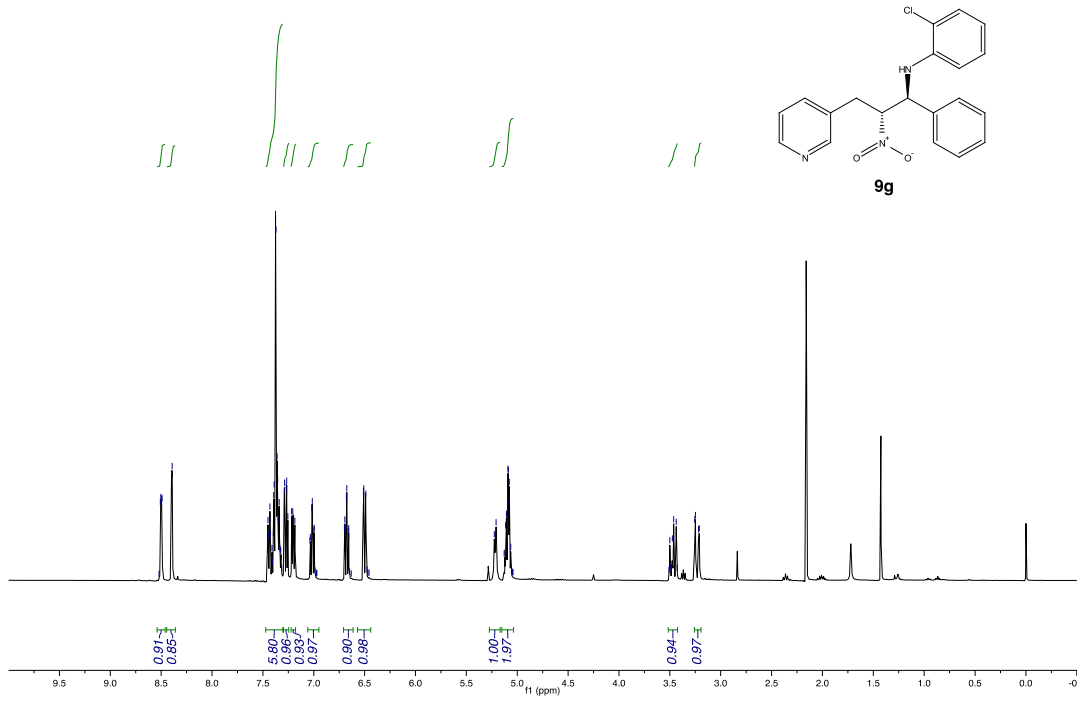
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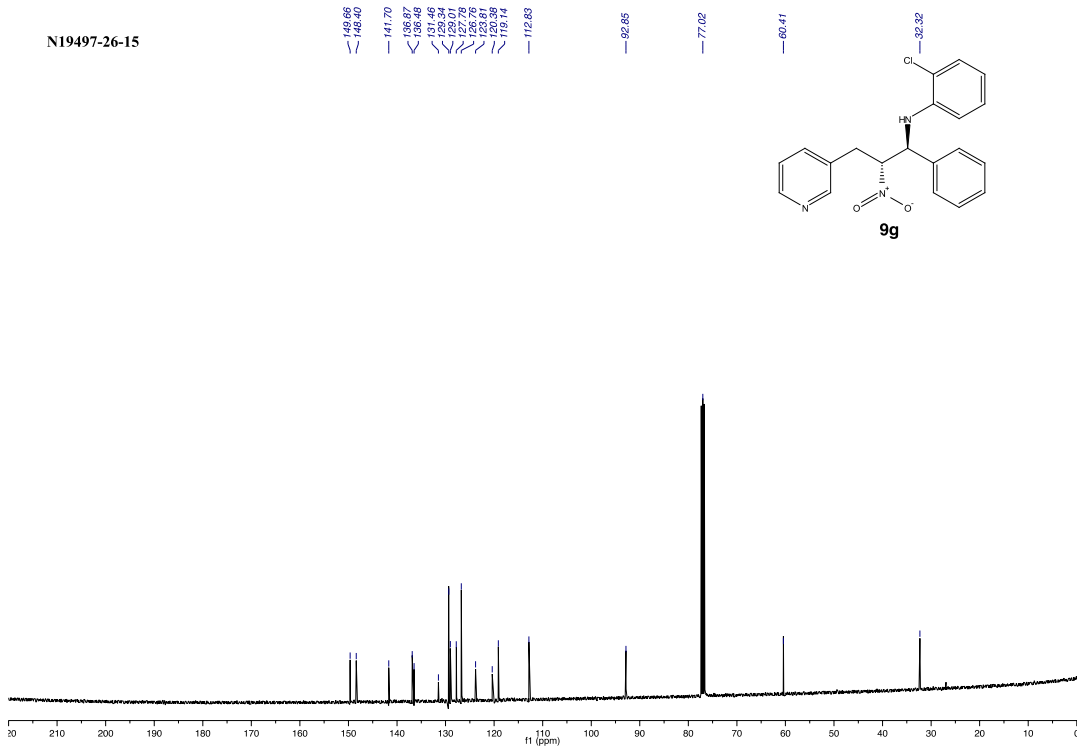
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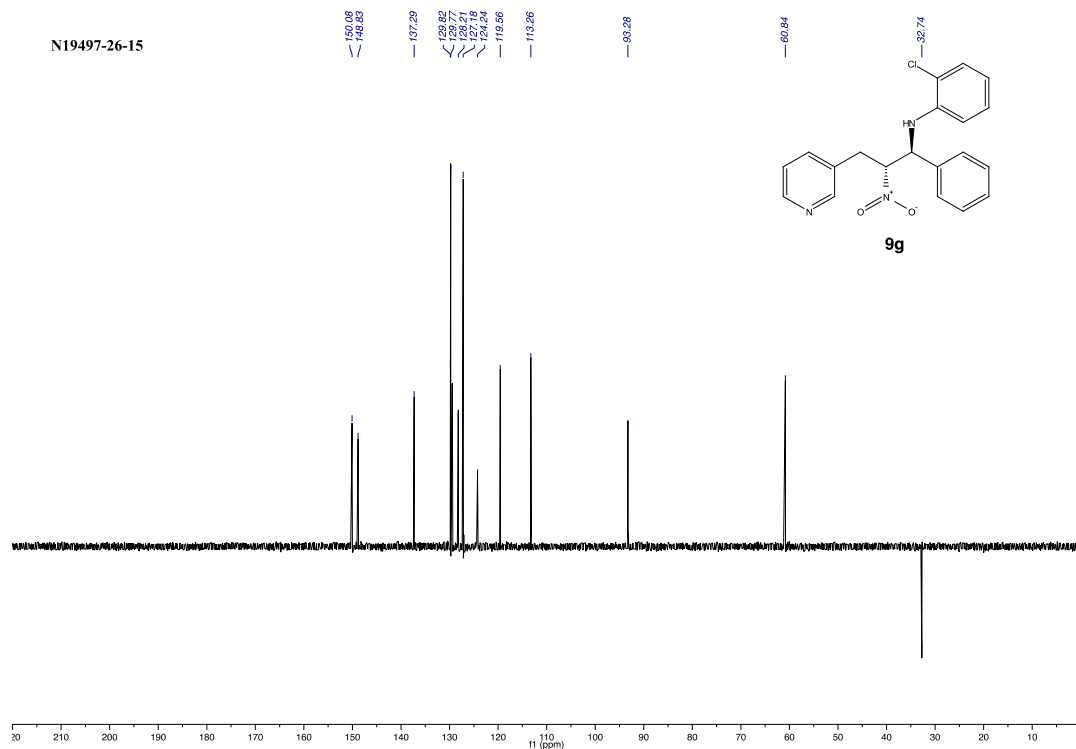
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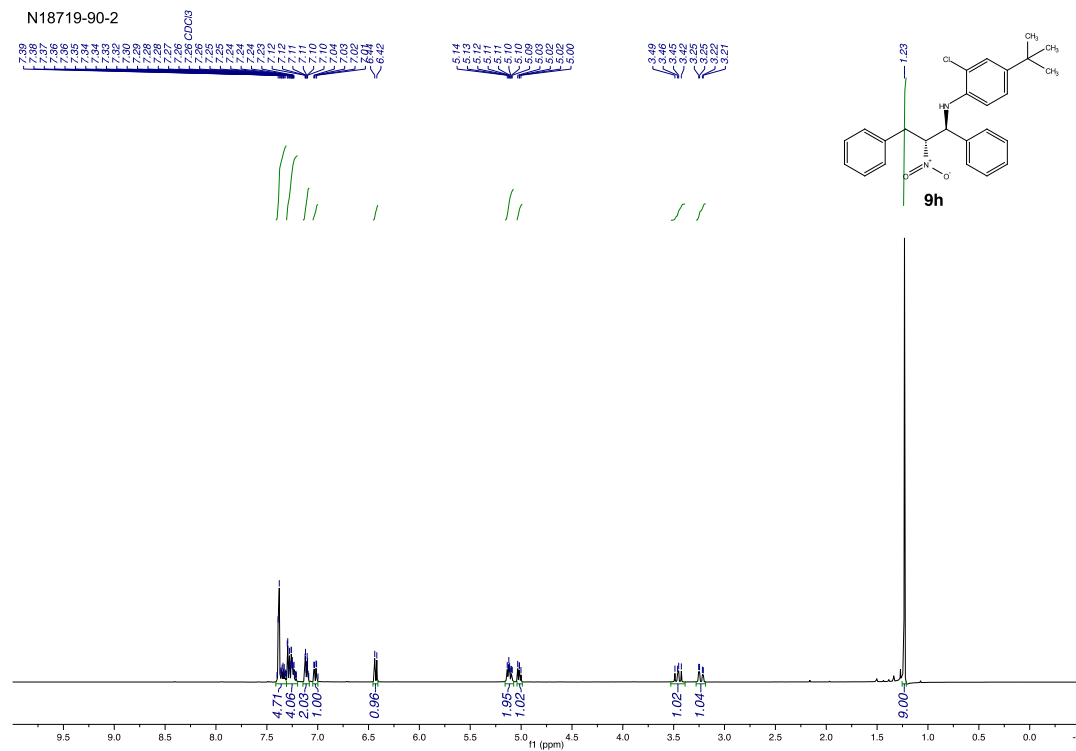
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N19497-26-15



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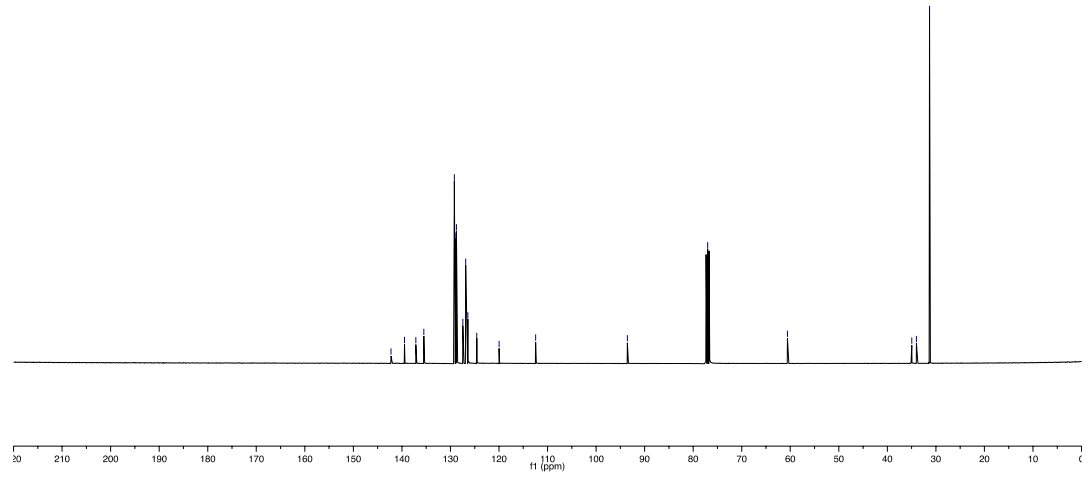
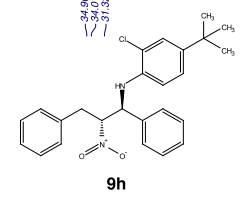


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137.12
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133.89
129.76
126.86
126.41
119.97
112.46

93.98
77.02
60.99

34.96
34.01
31.52

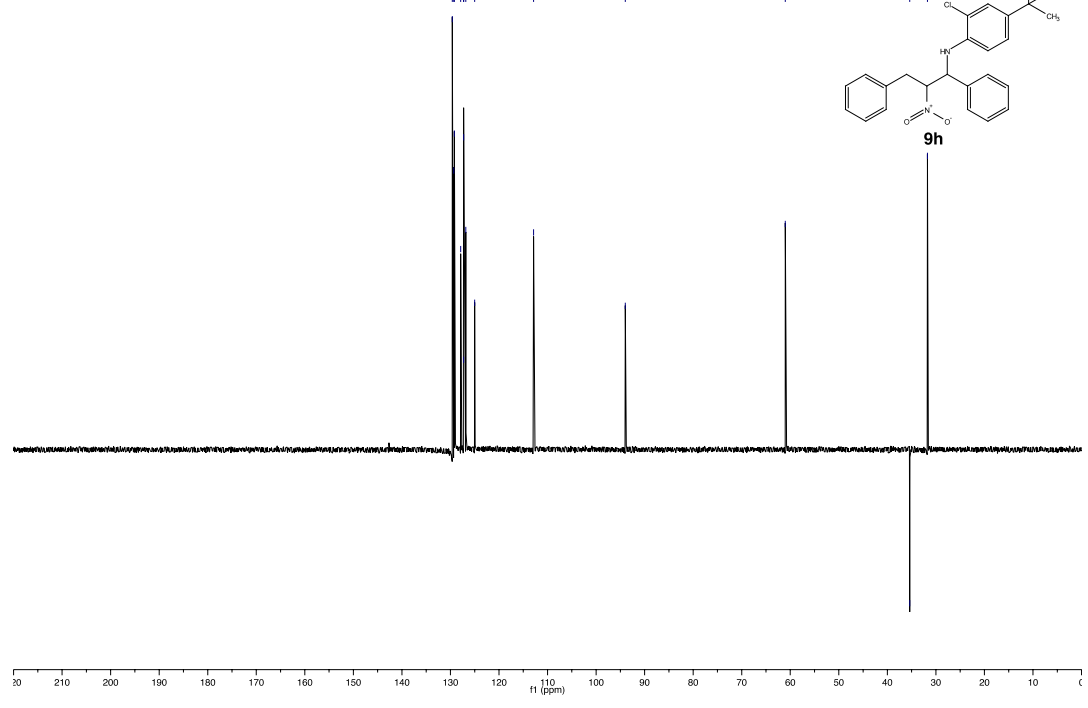
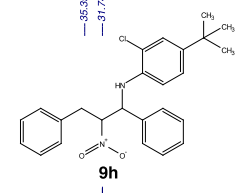


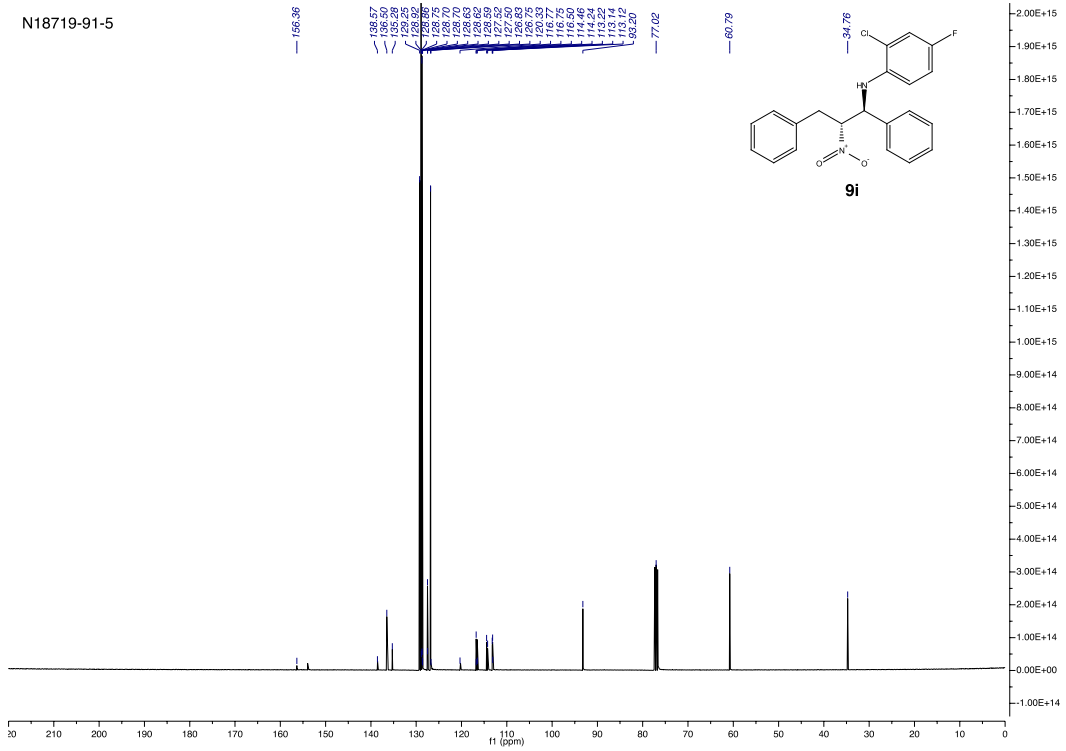
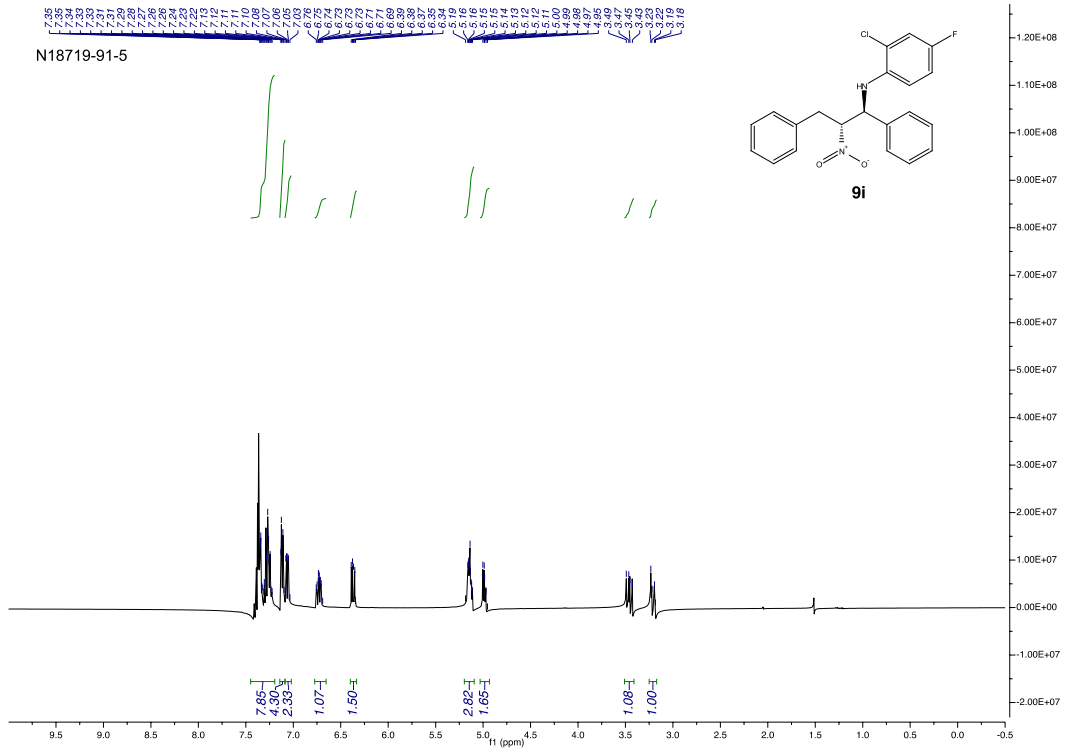
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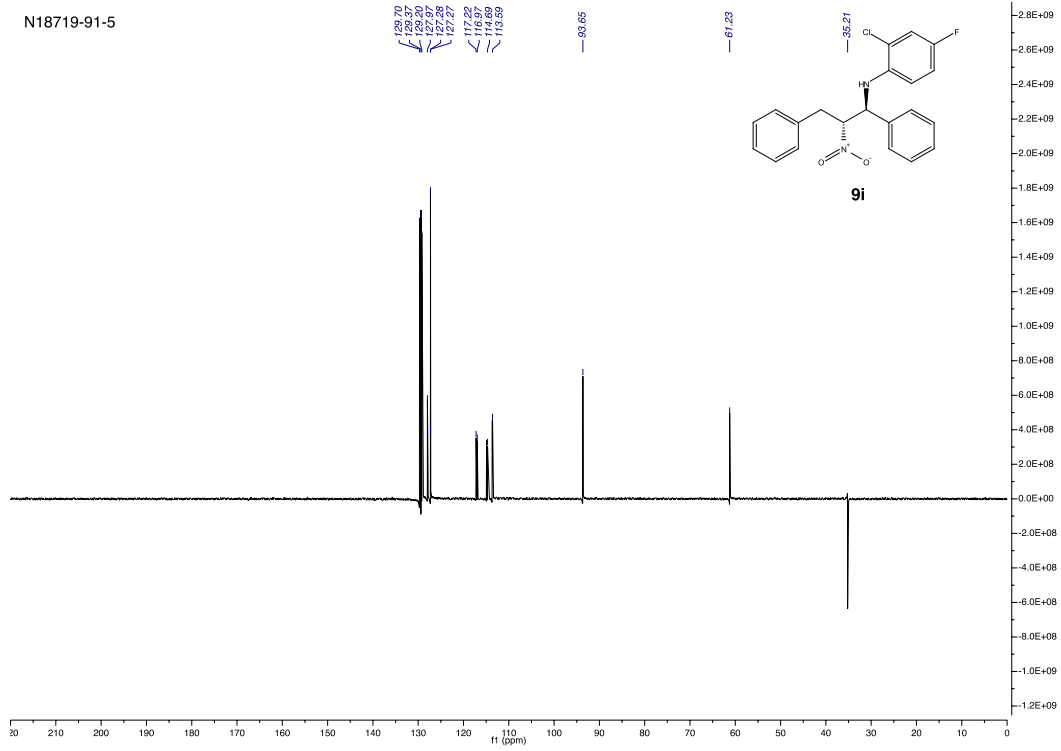
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61.02

35.99
31.74

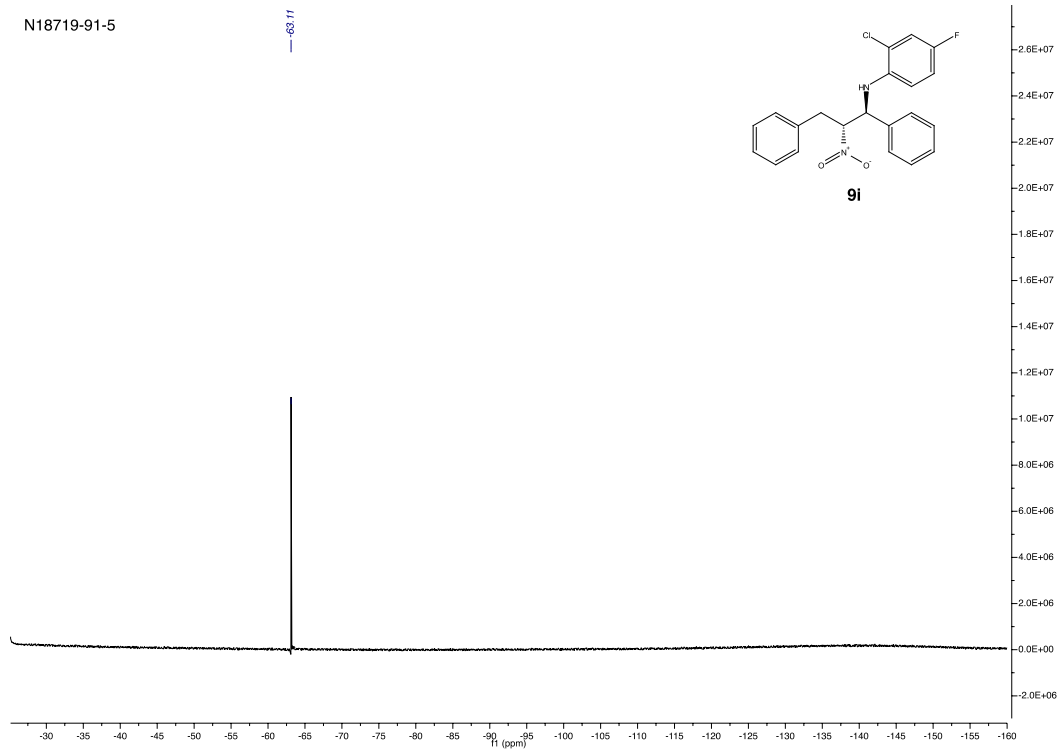




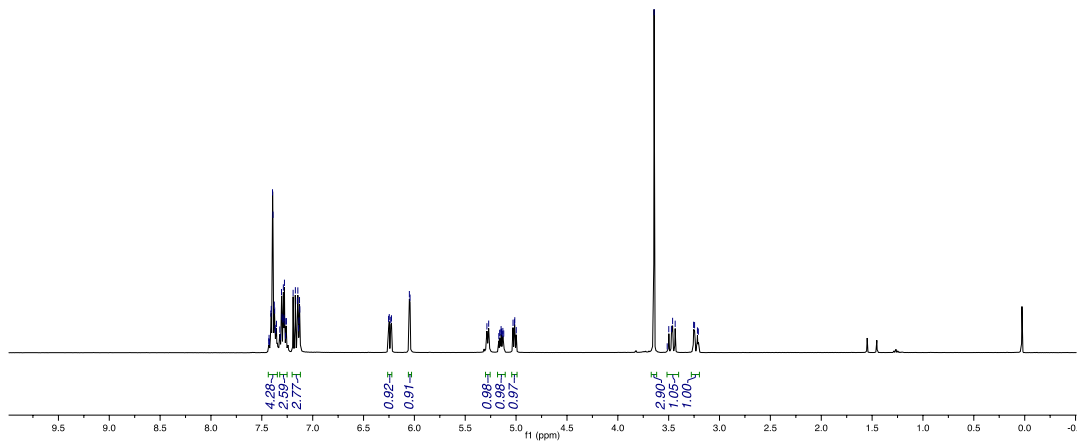
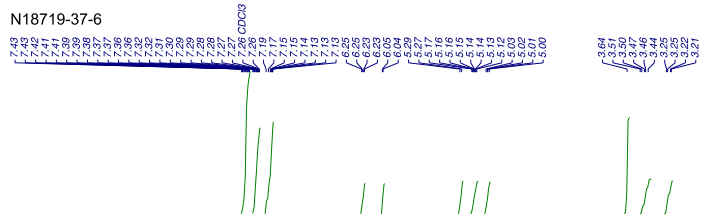
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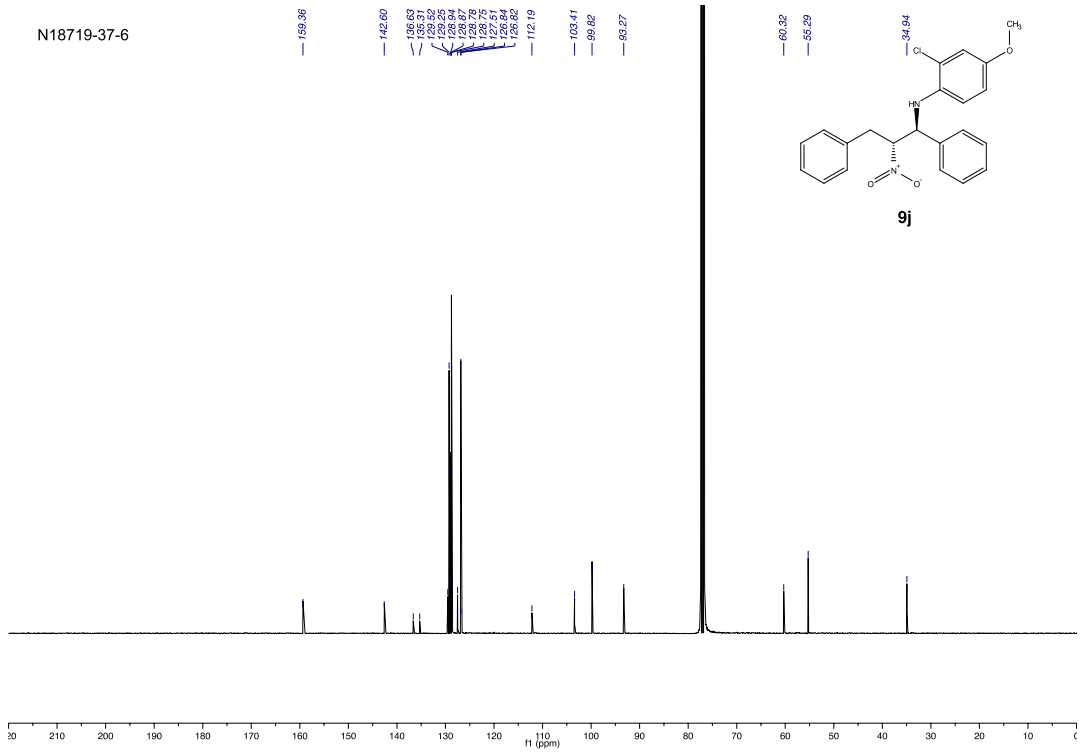
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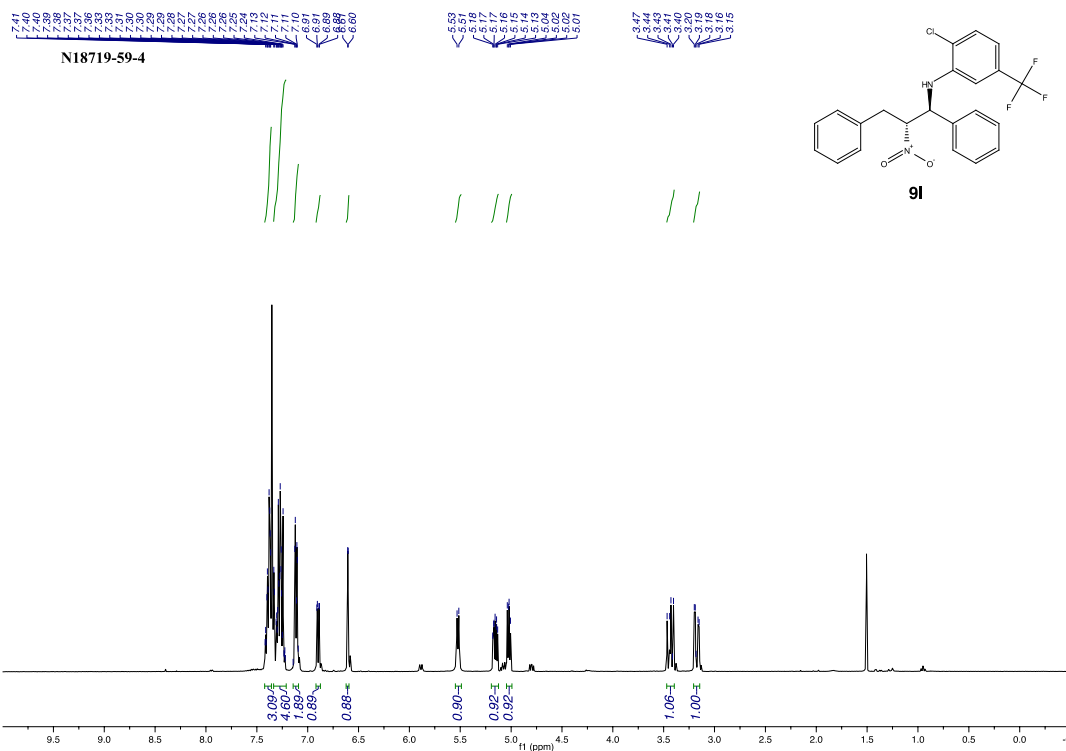
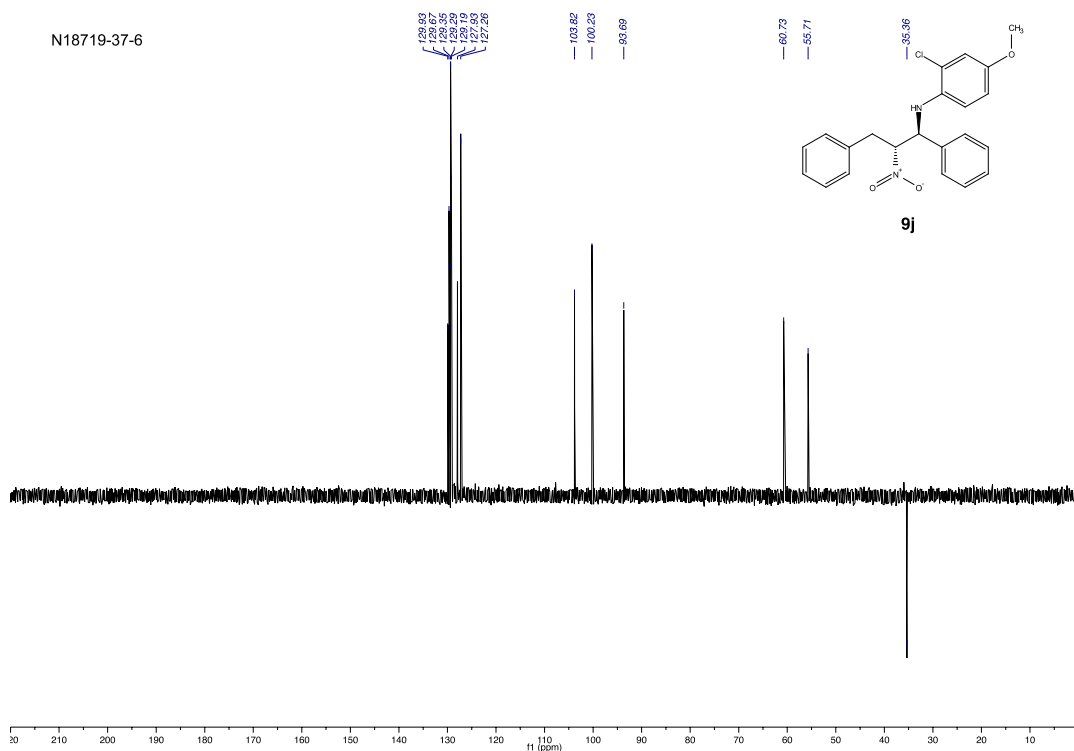
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N18719-37-6



N18719-37-6



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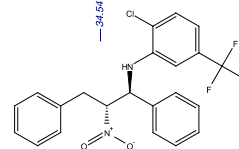
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126.19
115.64
109.20
108.65

92.36

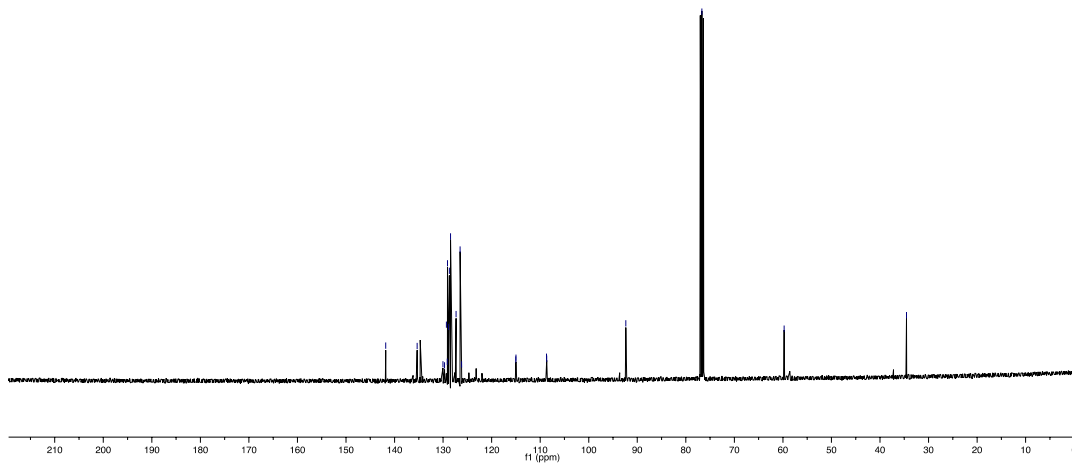
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59.75

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91



N18719-59-4

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129.85
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128.05

115.76

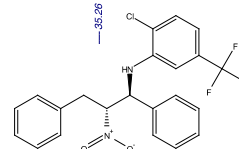
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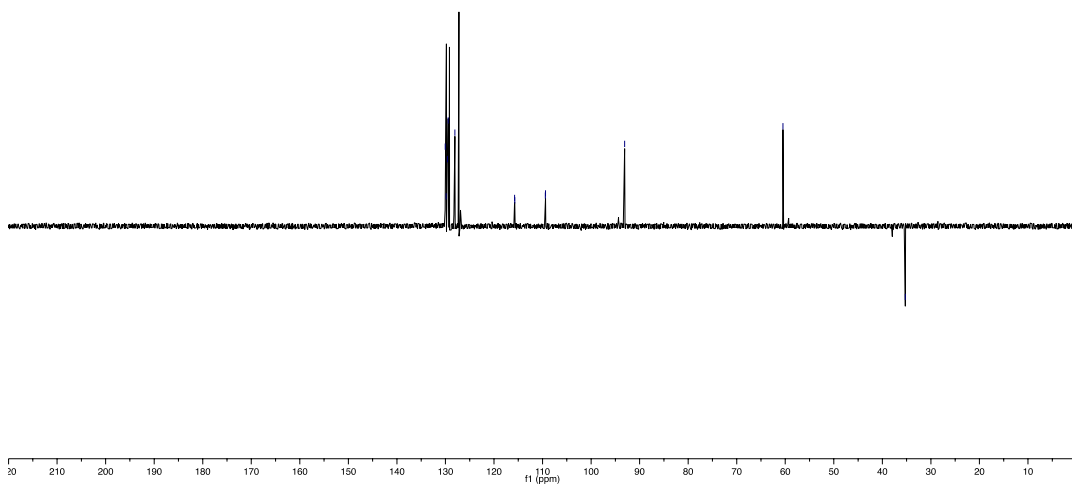
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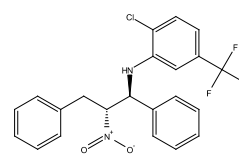
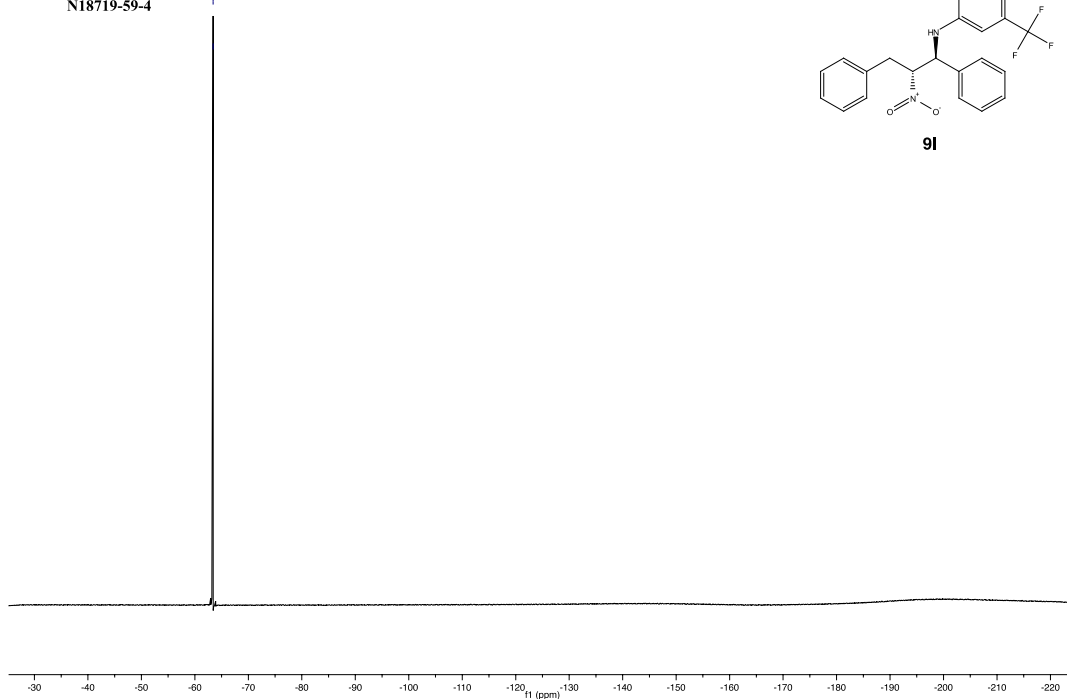


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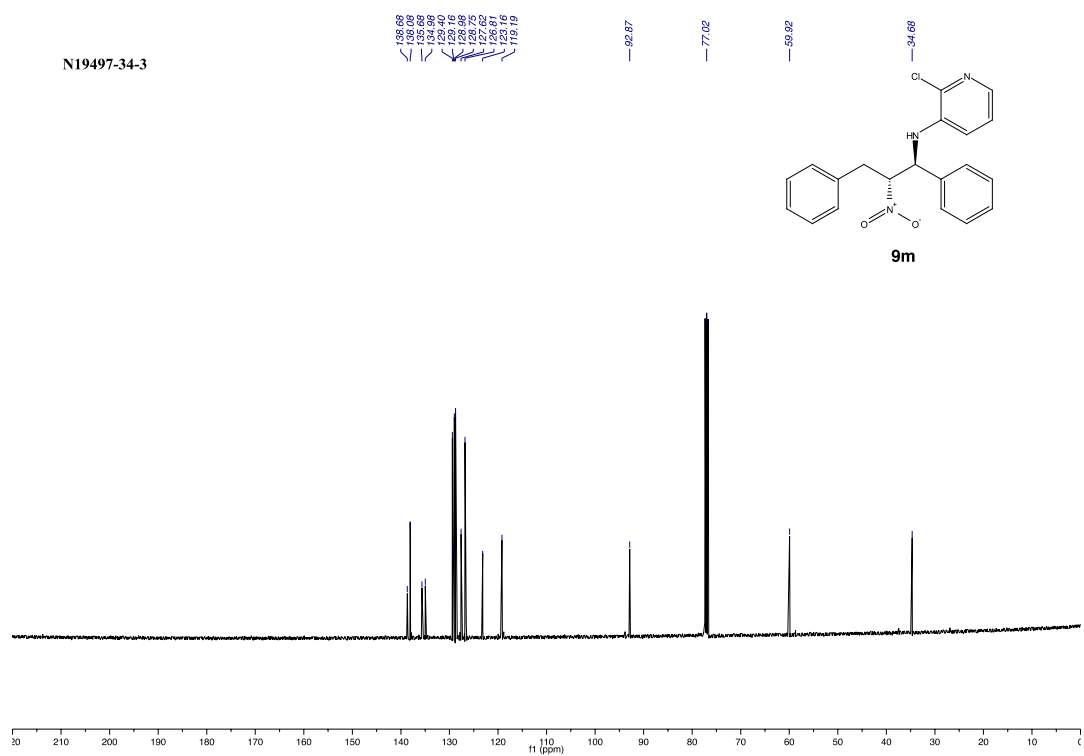
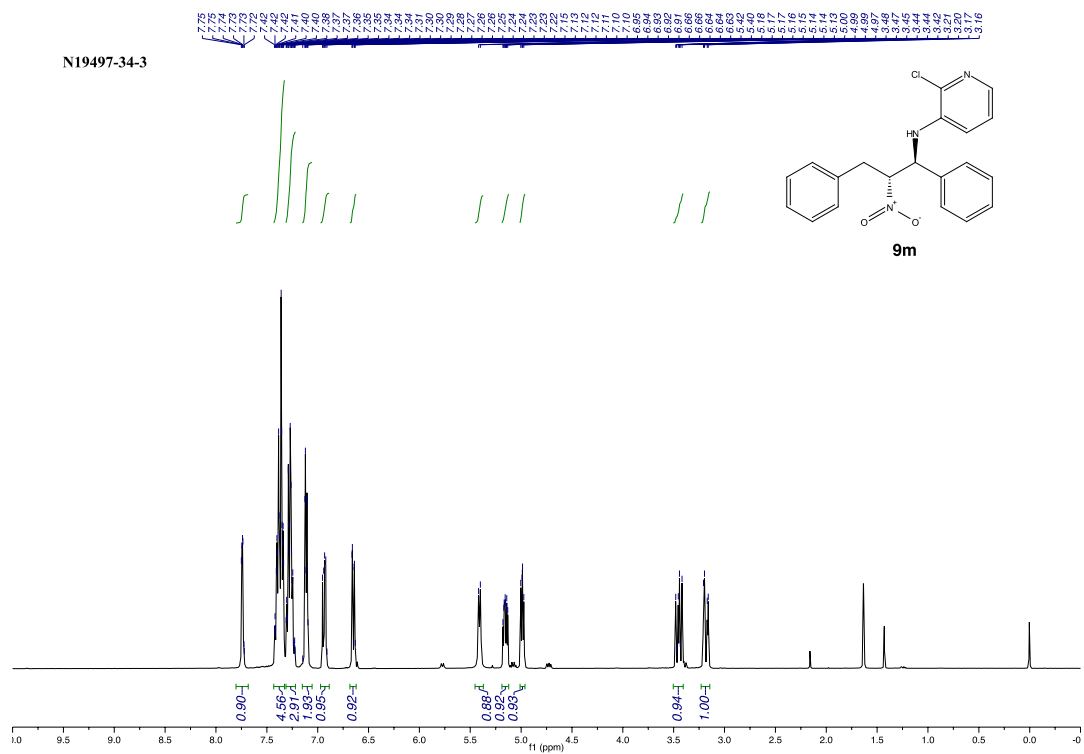


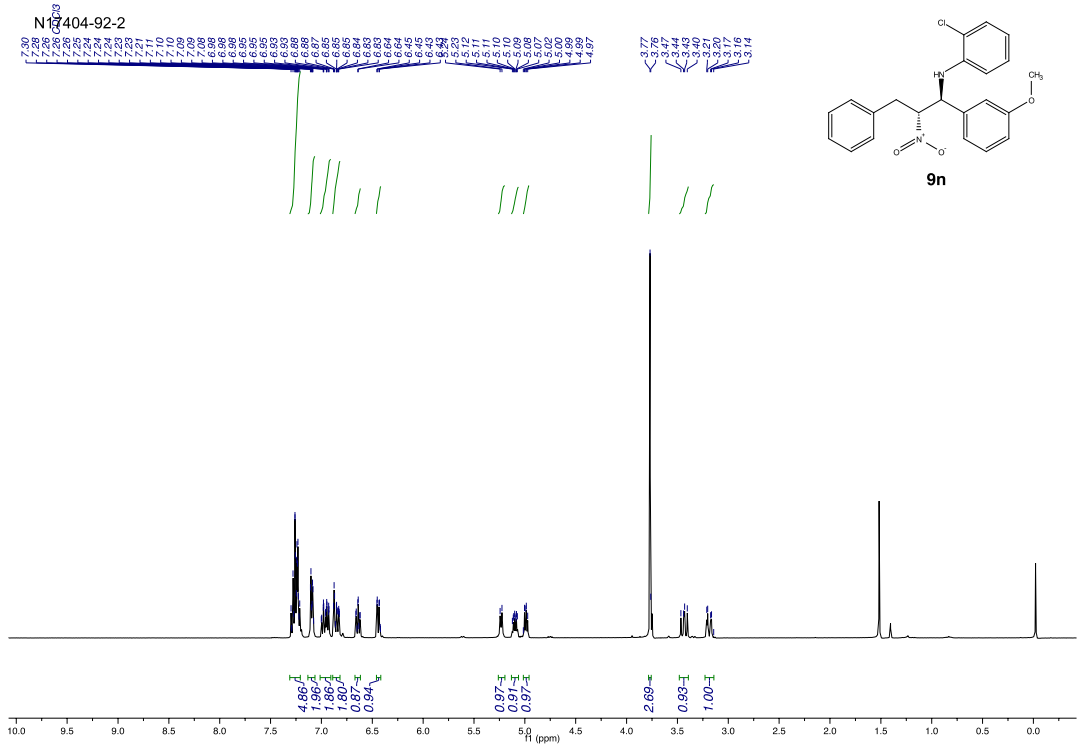
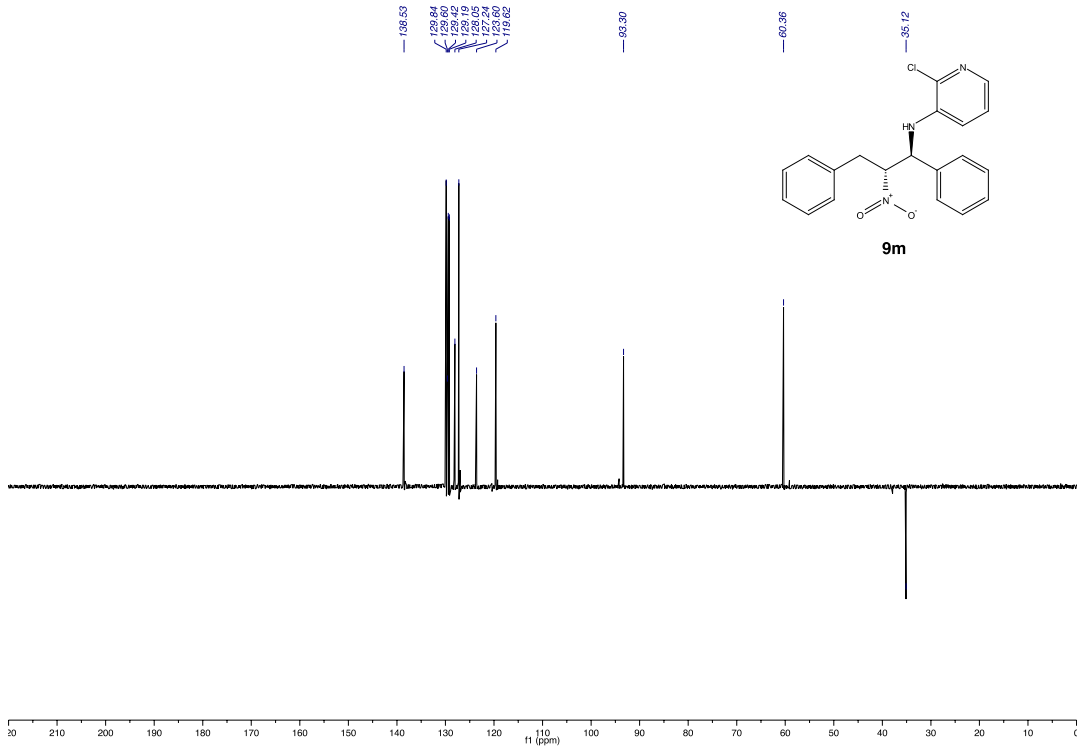
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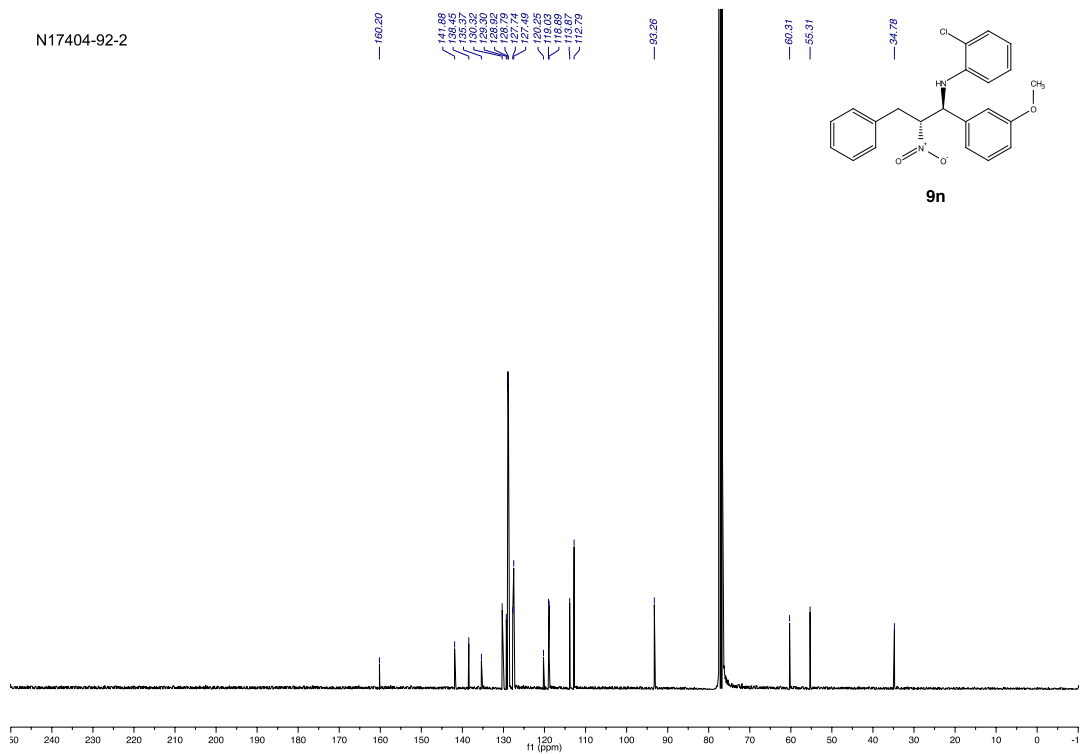


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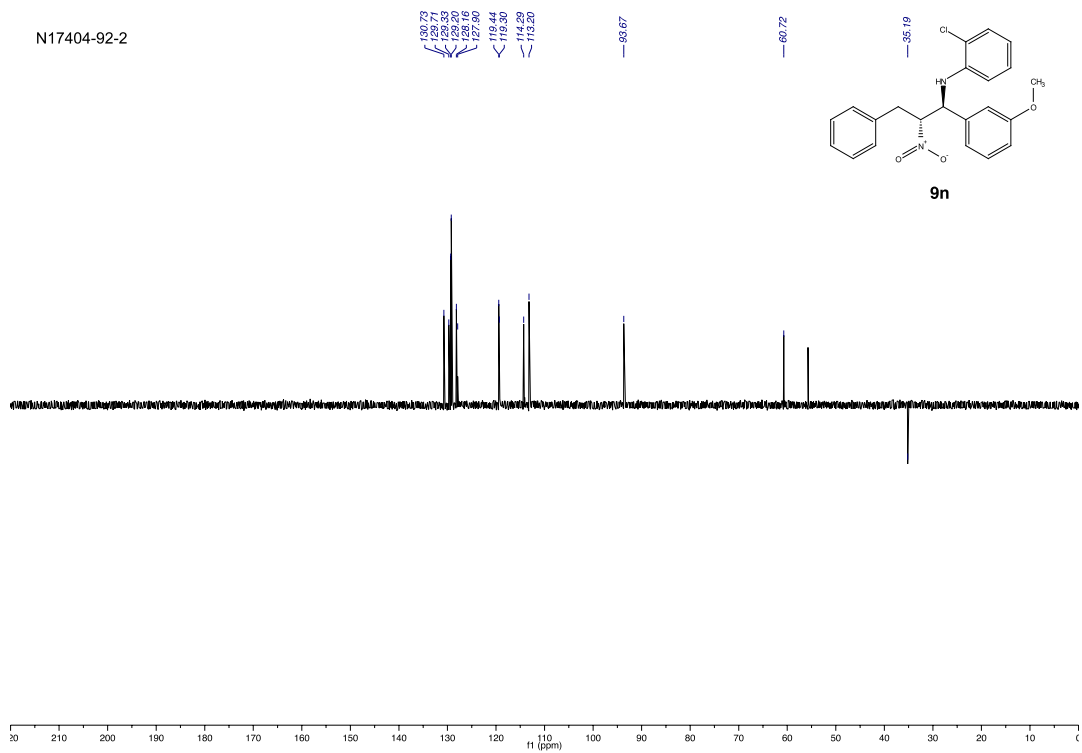




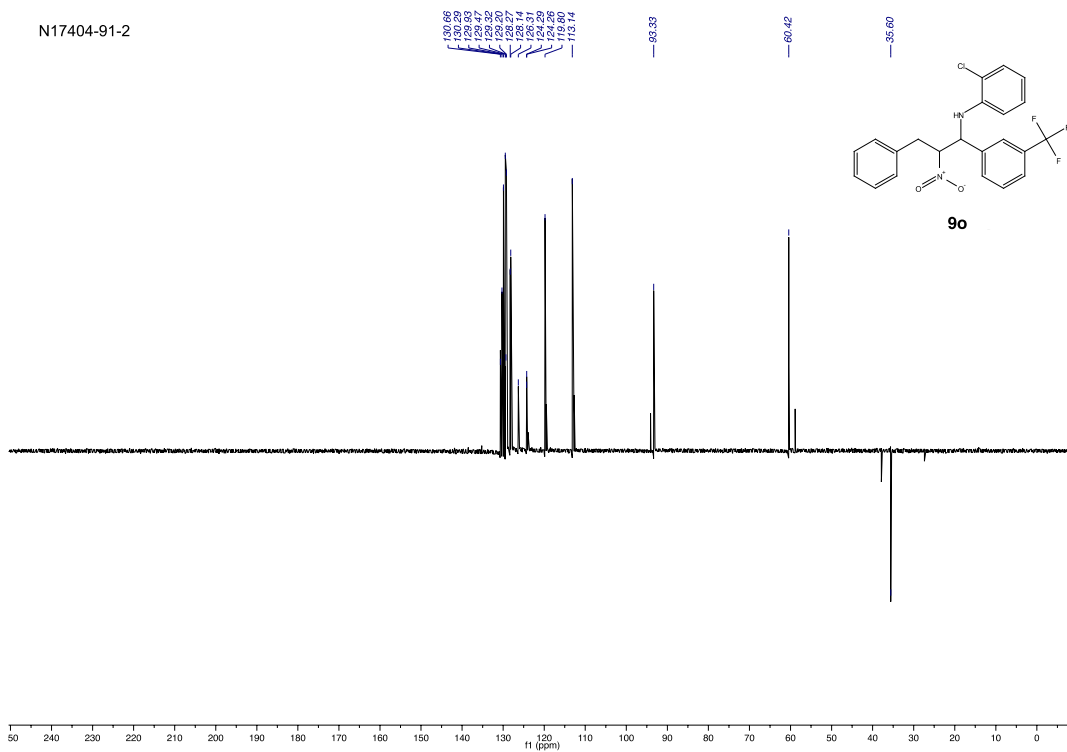
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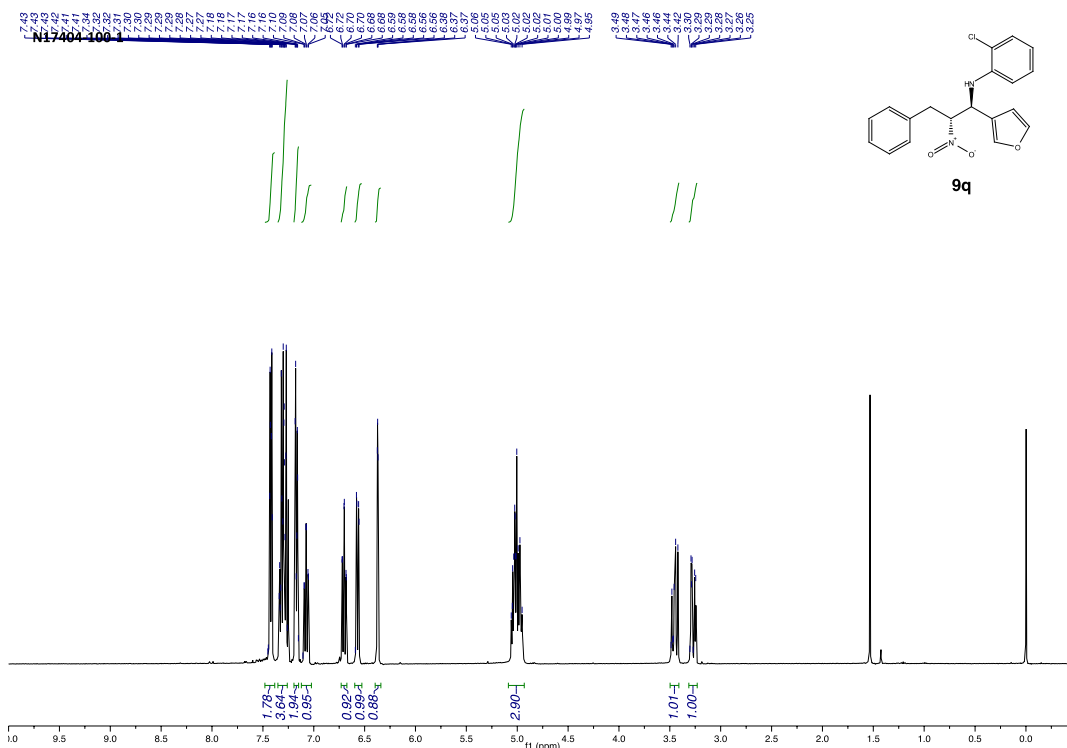
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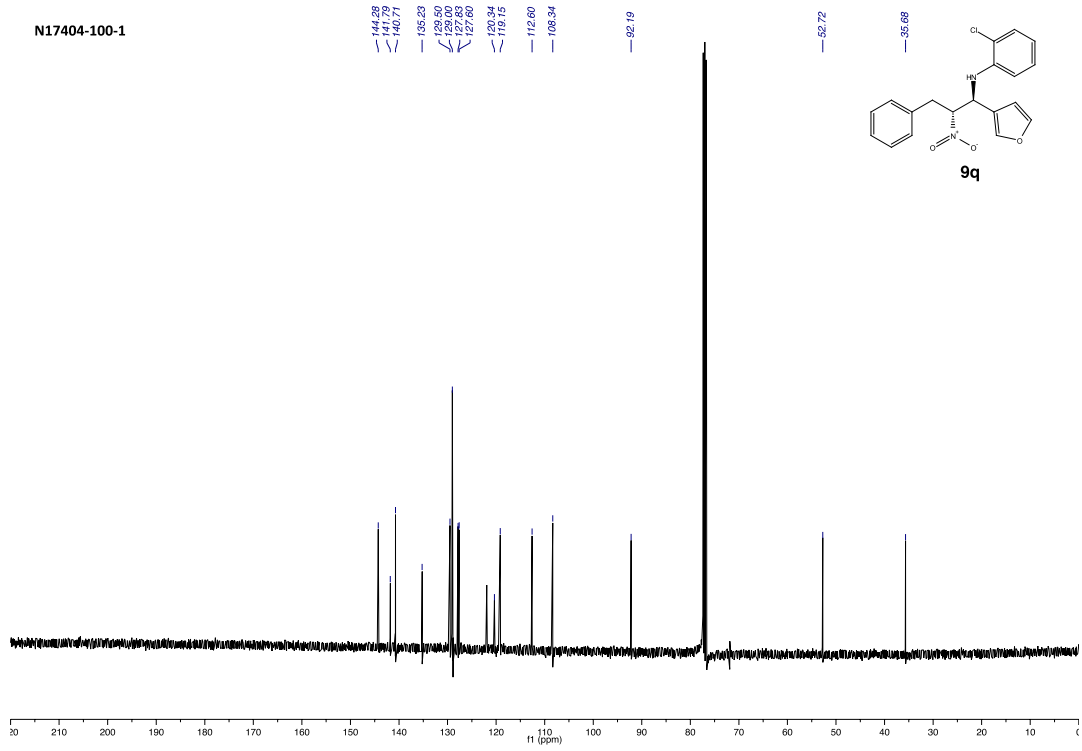
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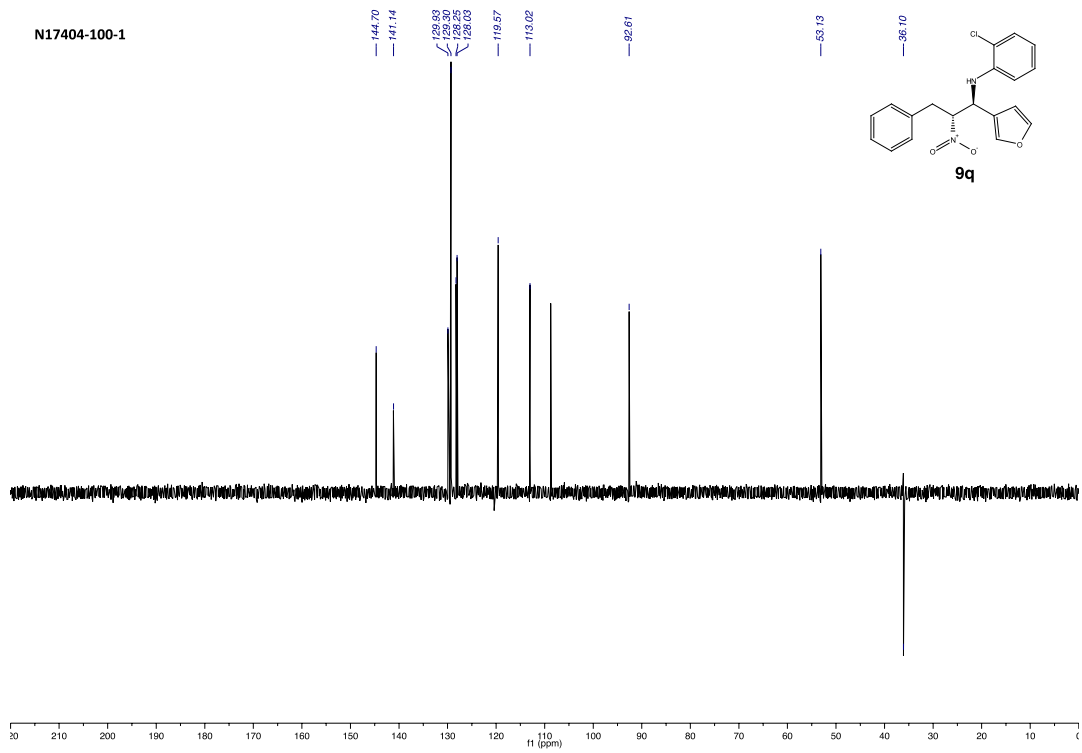
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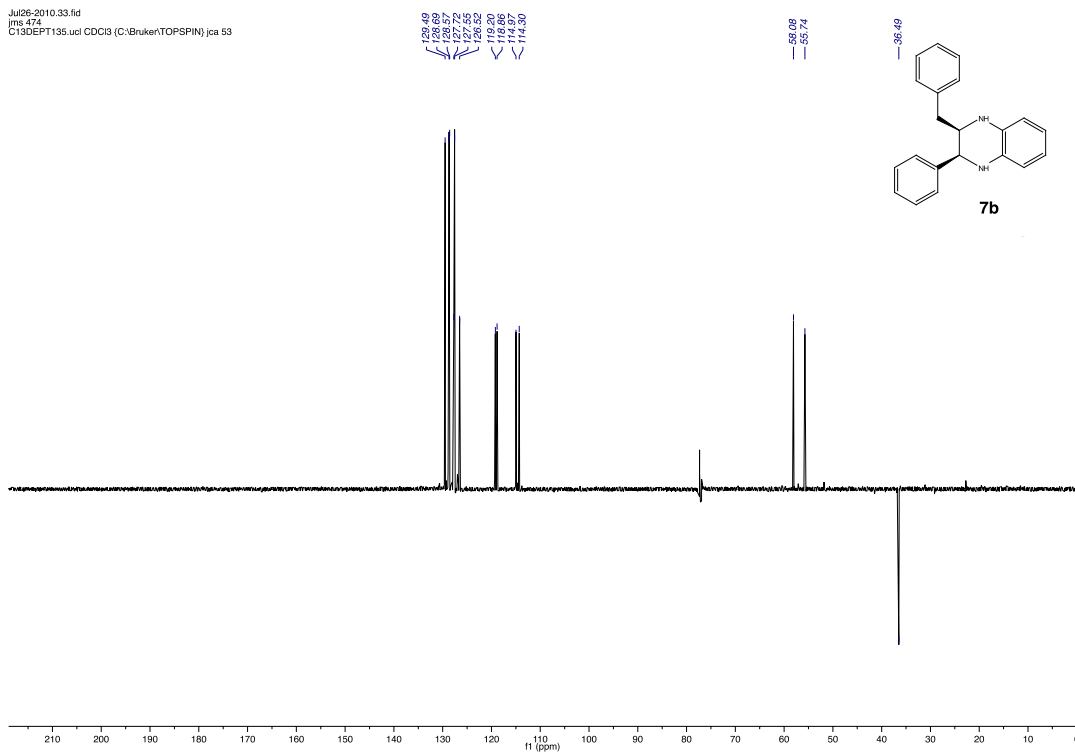
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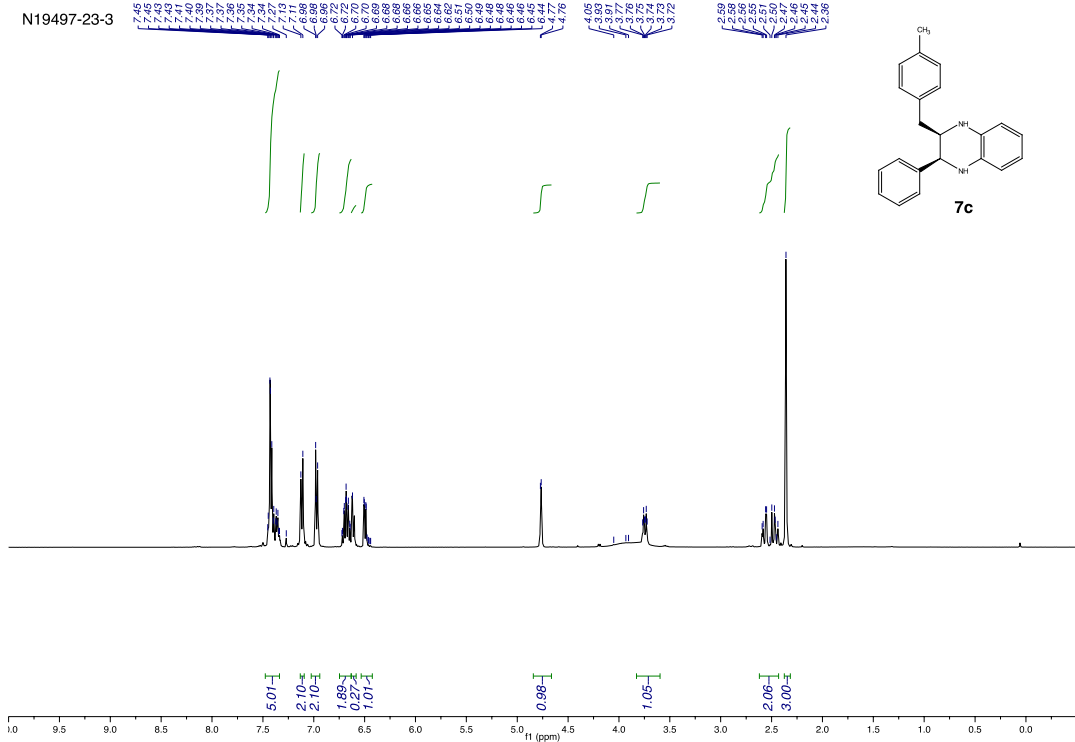
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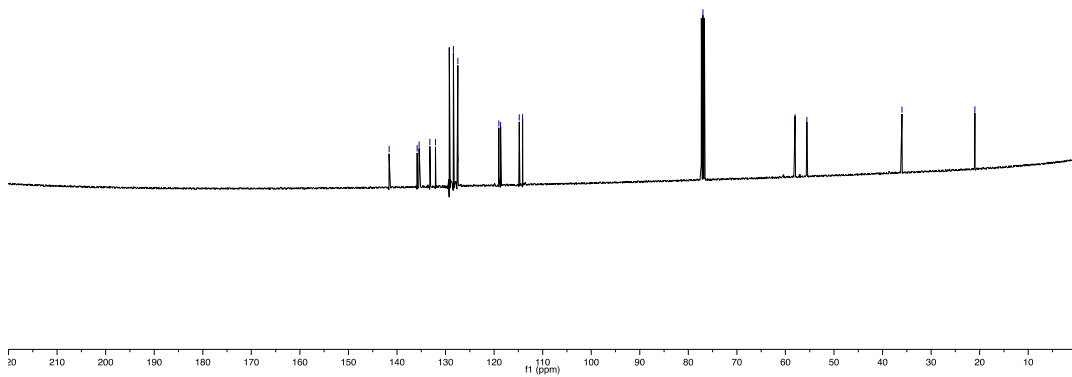
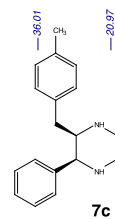


N19497-23-3

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129.20
129.07
127.44
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118.66
114.13

77.00

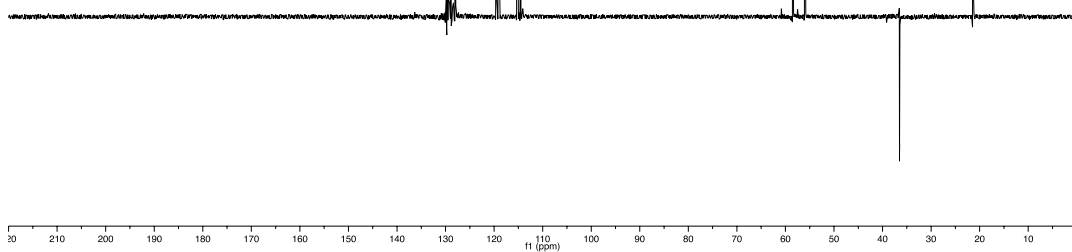
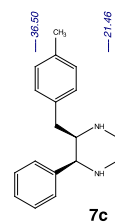
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55.89

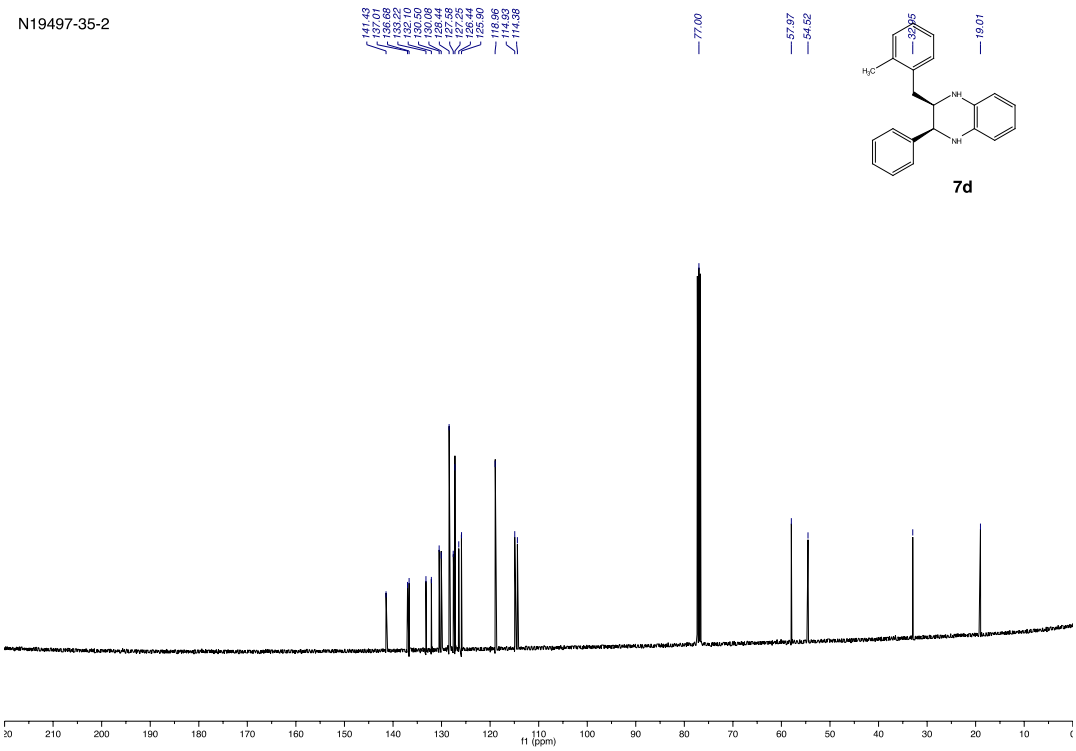
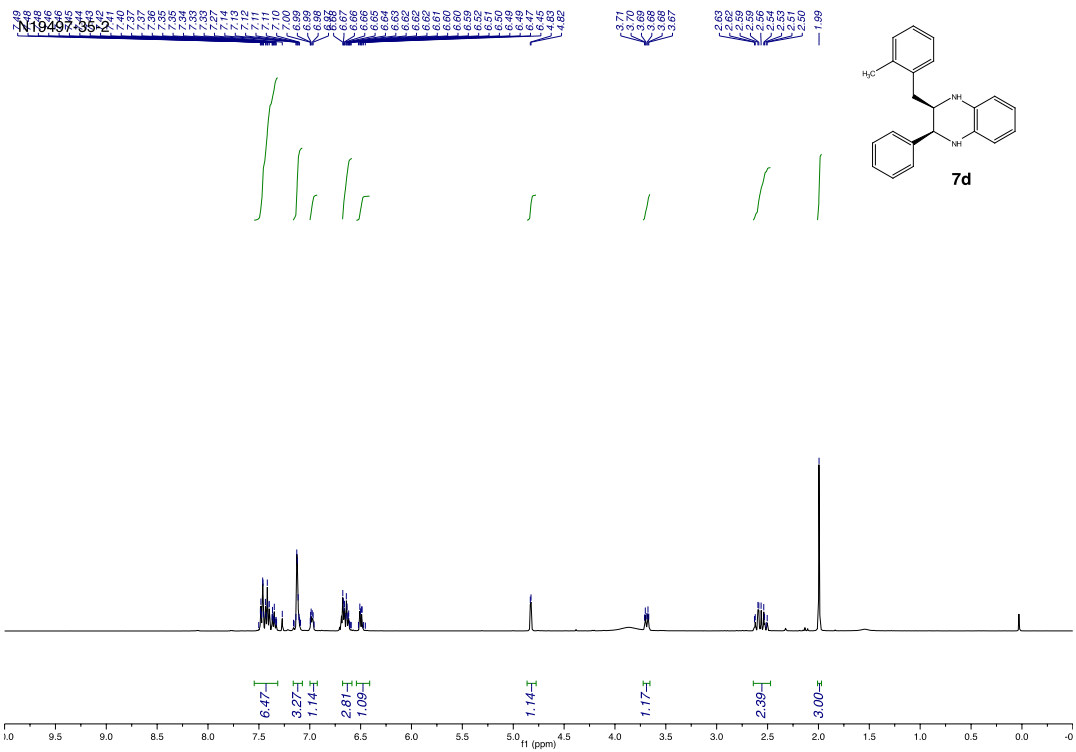


N19497-23-3

128.68
127.95
119.52
118.15
114.62

58.51
56.07

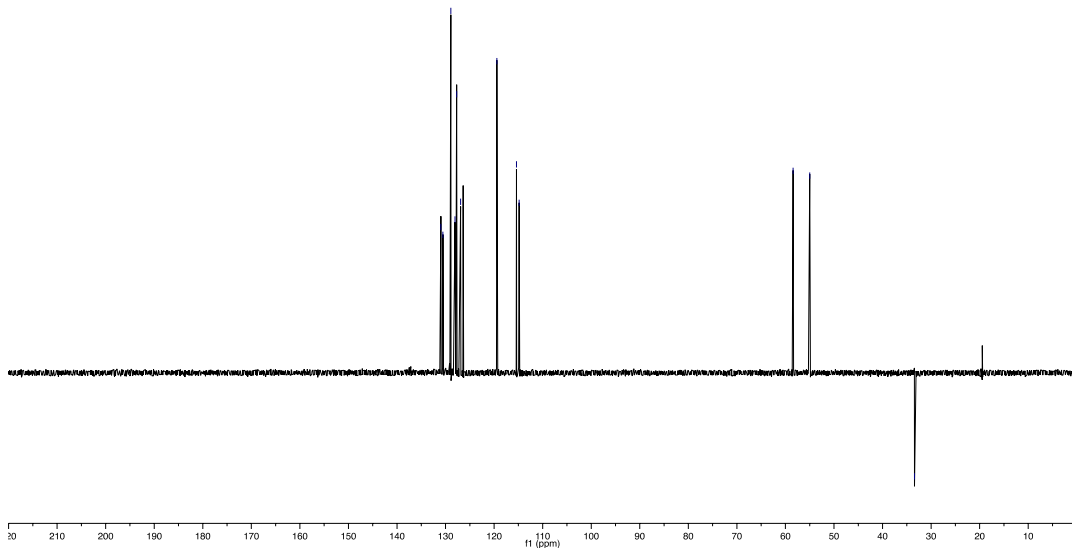
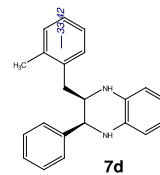




N19497-35-2

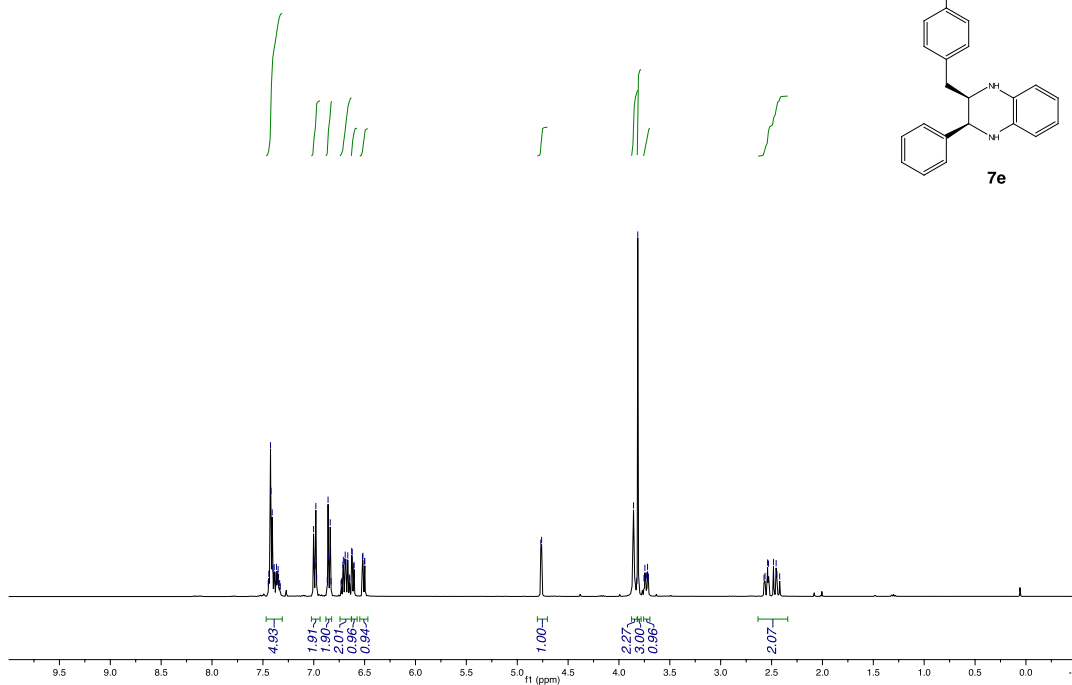
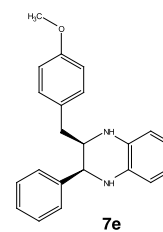
130.97
128.90
128.05
126.91
119.43
115.40
114.84

58.44
54.89

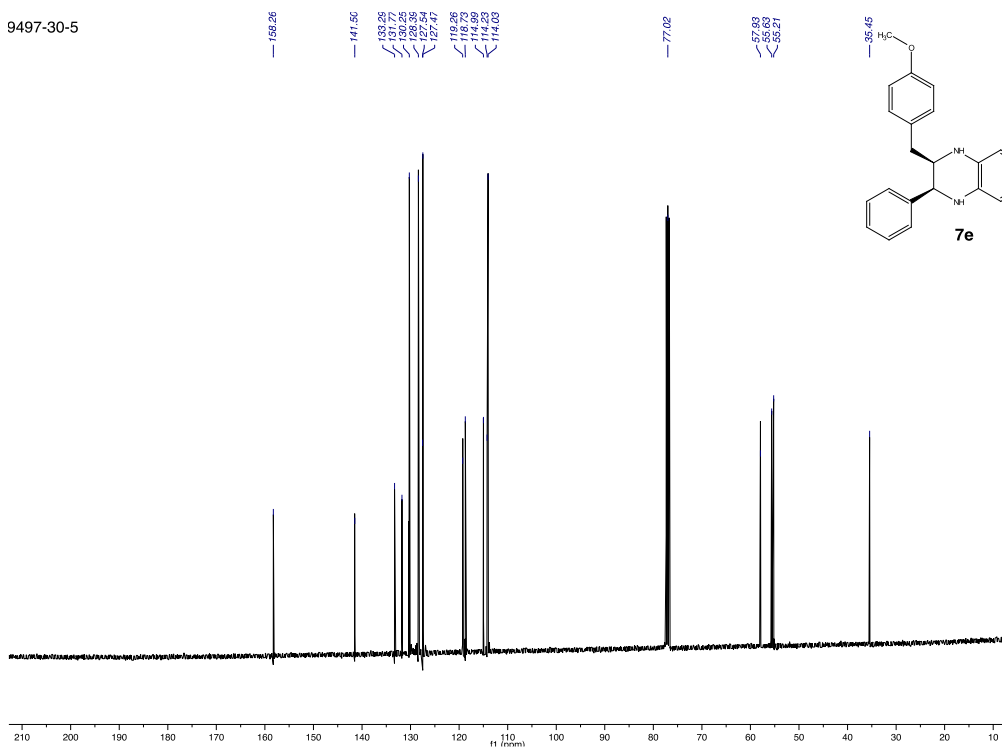


N19497-30-5

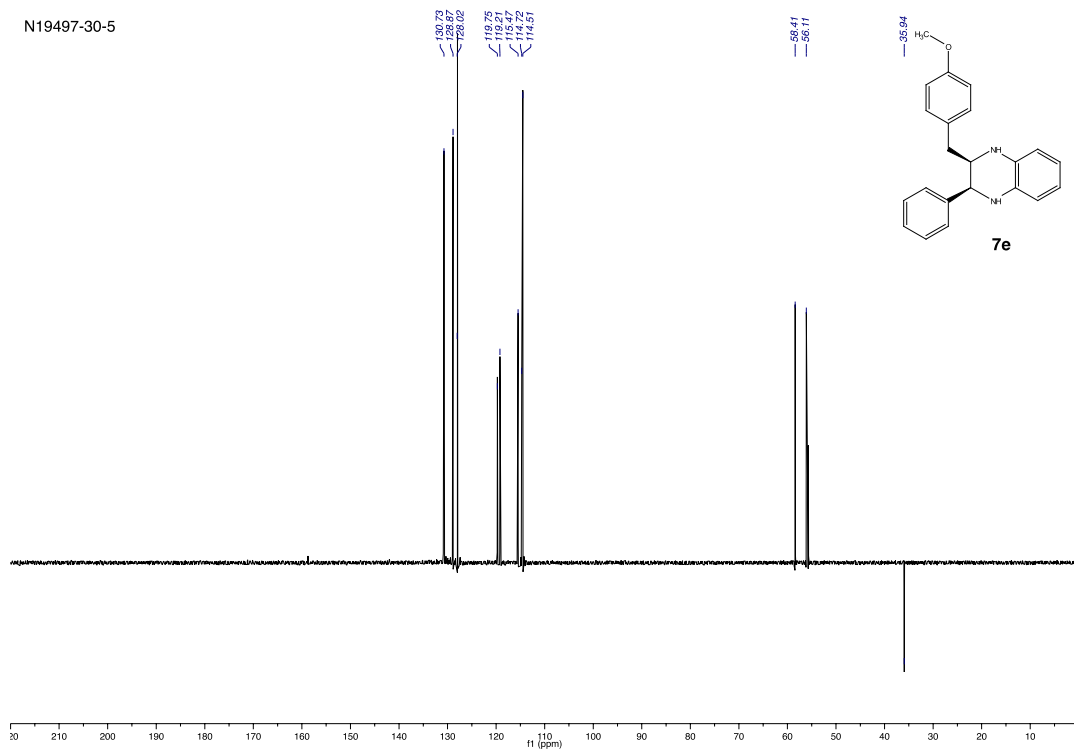
7.45
7.43
7.42
7.40
7.39
7.37
7.36
7.35
7.34
7.00
6.98
6.97
6.96
6.85
6.84
6.63
6.73
6.71
6.70
6.67
6.65
6.65
6.62
6.61
6.52
6.52
6.50
4.77
3.86
3.82
3.75
3.72
3.72
3.71
3.57
3.56
3.54
3.48
3.45
2.42

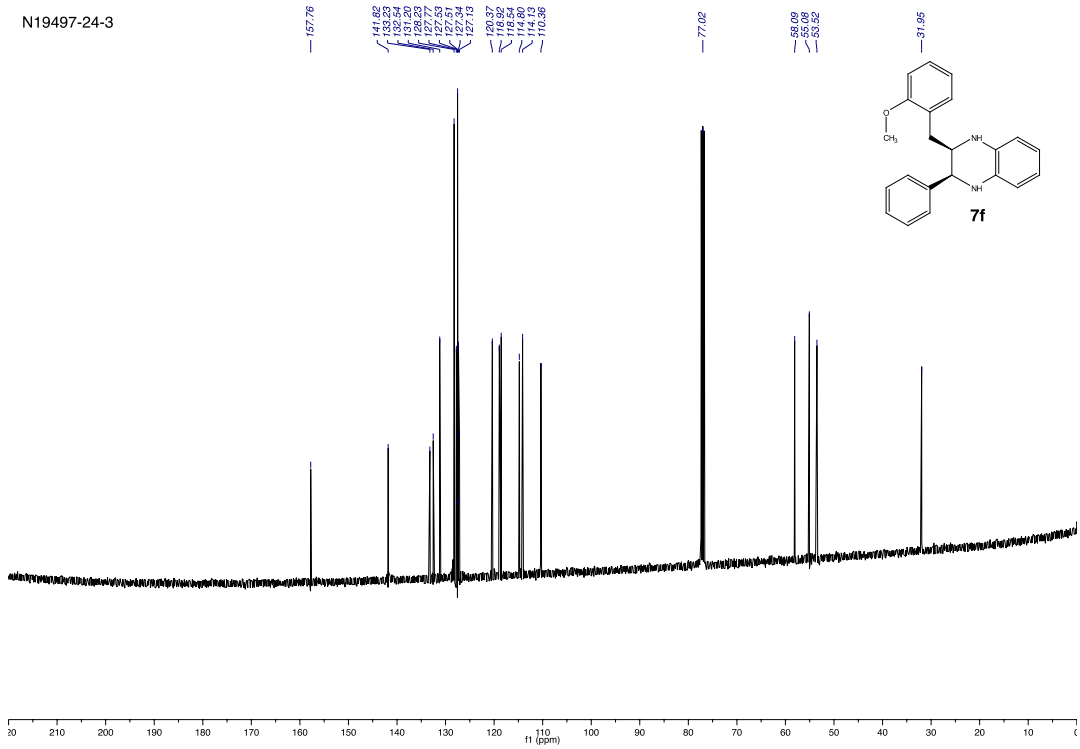
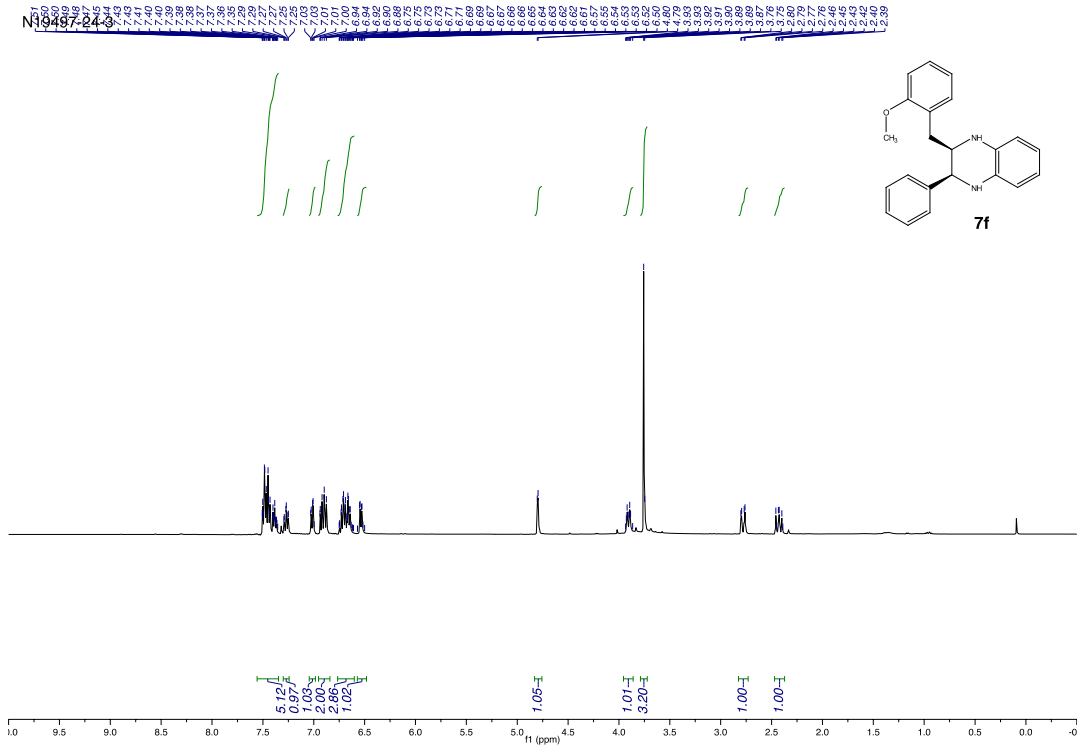


9497-30-5

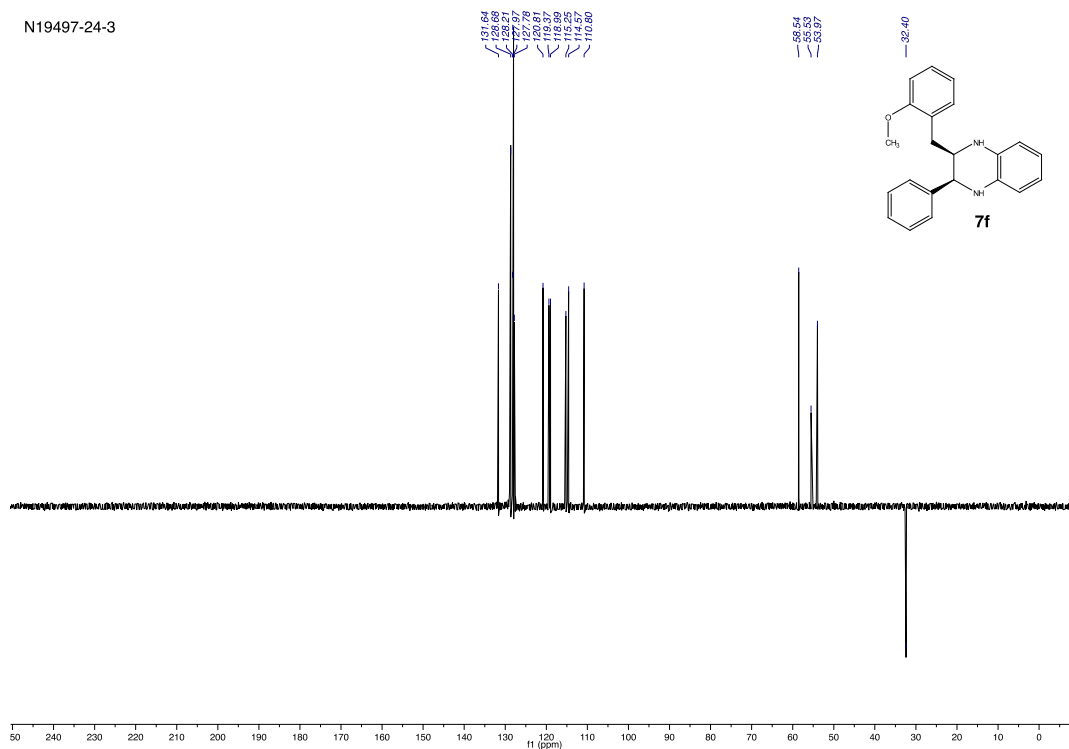


N19497-30-5

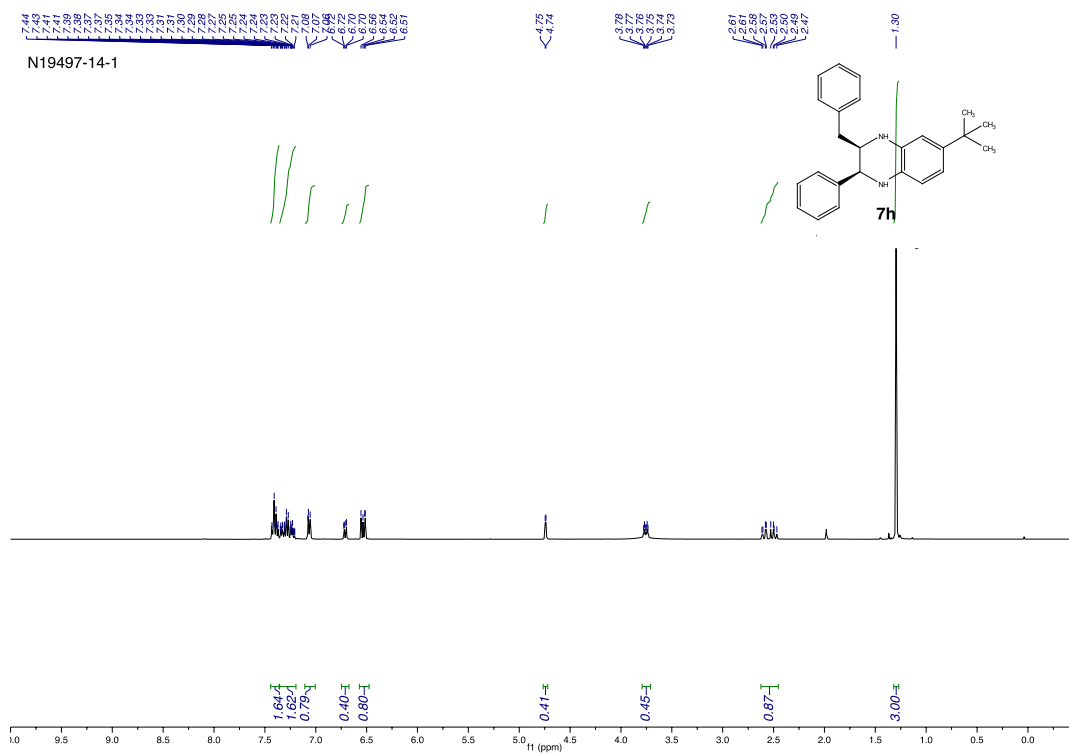




N19497-24-3



N19497-14-1



N19497-14-1

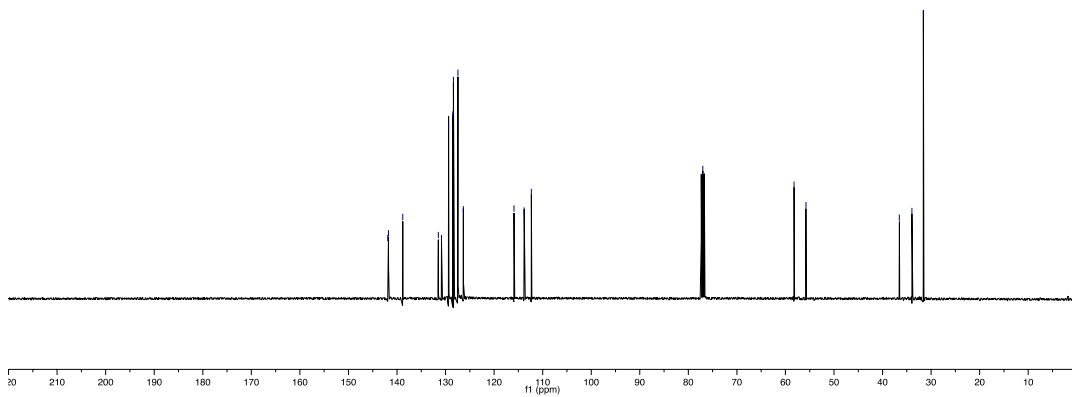
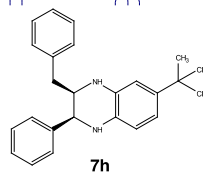
141.89
141.75
138.62
137.87
130.84
129.39
128.39
127.45
126.34

115.91
113.62
112.32

77.02

58.22
55.78

36.54
31.55



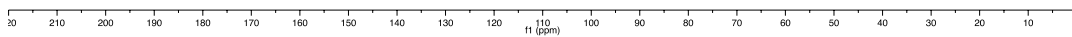
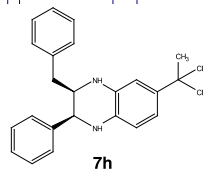
N19497-14-1

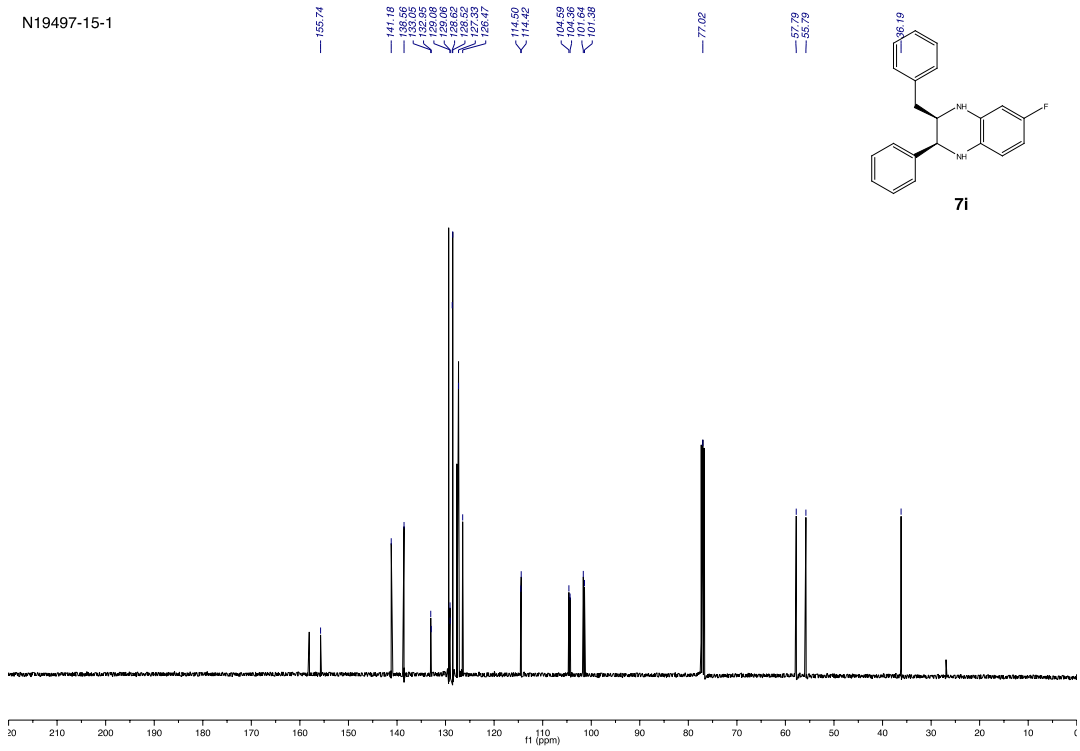
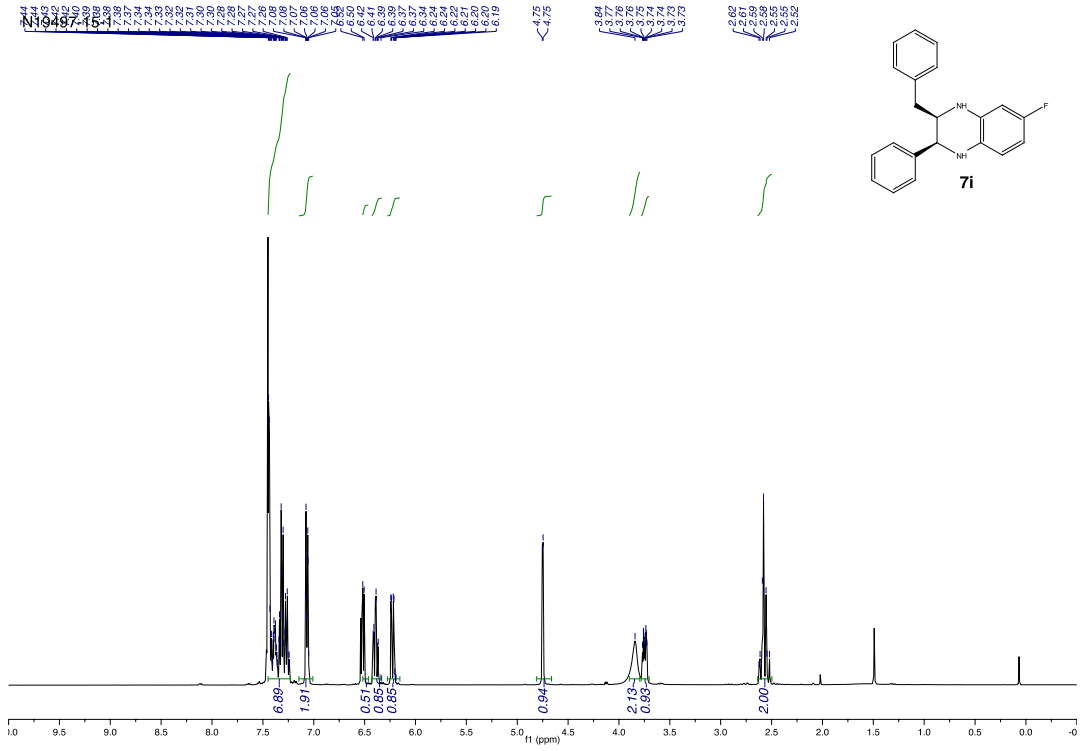
129.88
129.01
128.89
126.83

116.40
114.31
112.81

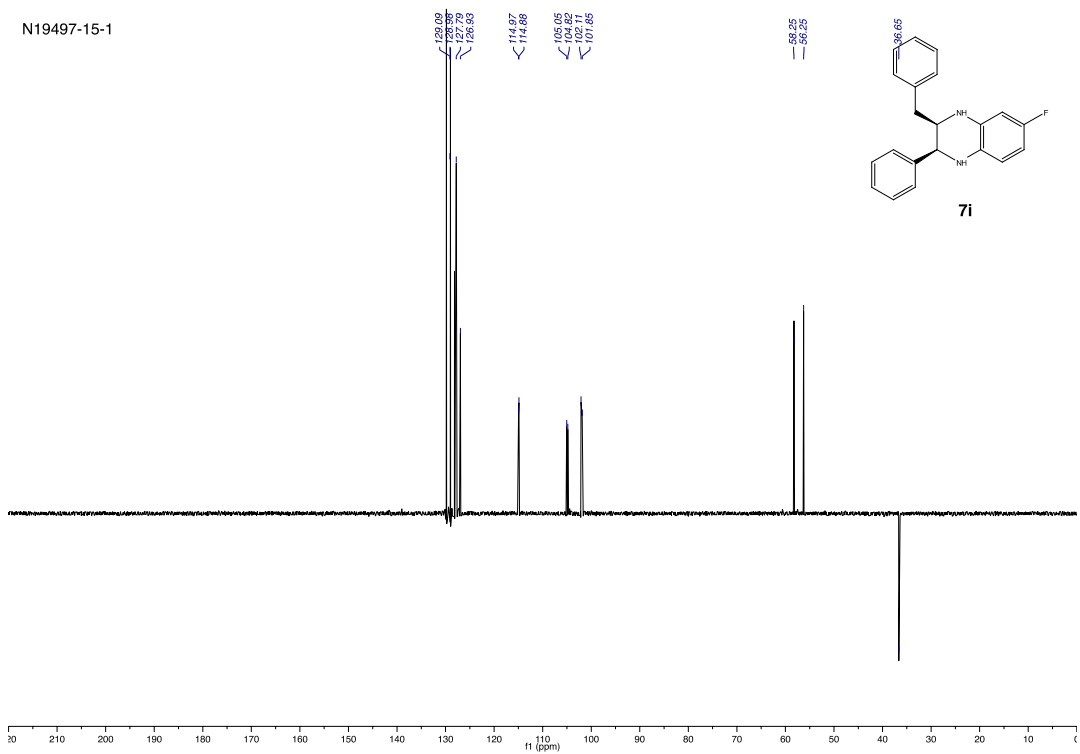
58.71
55.27

37.03
32.08

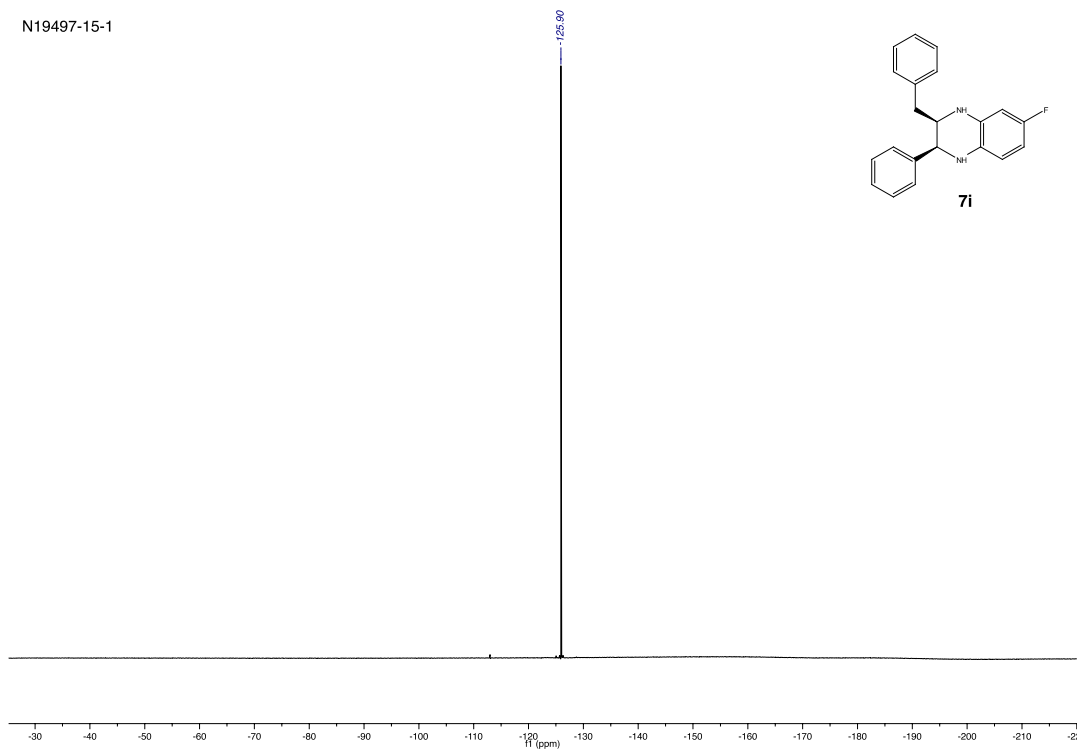




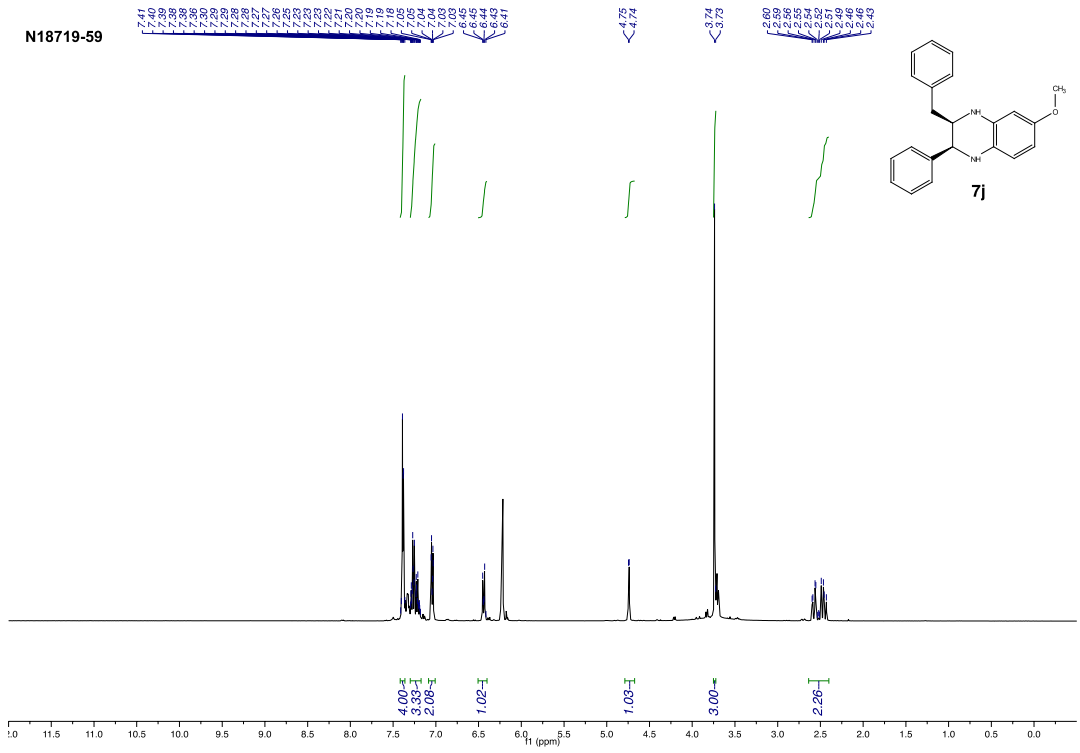
N19497-15-1



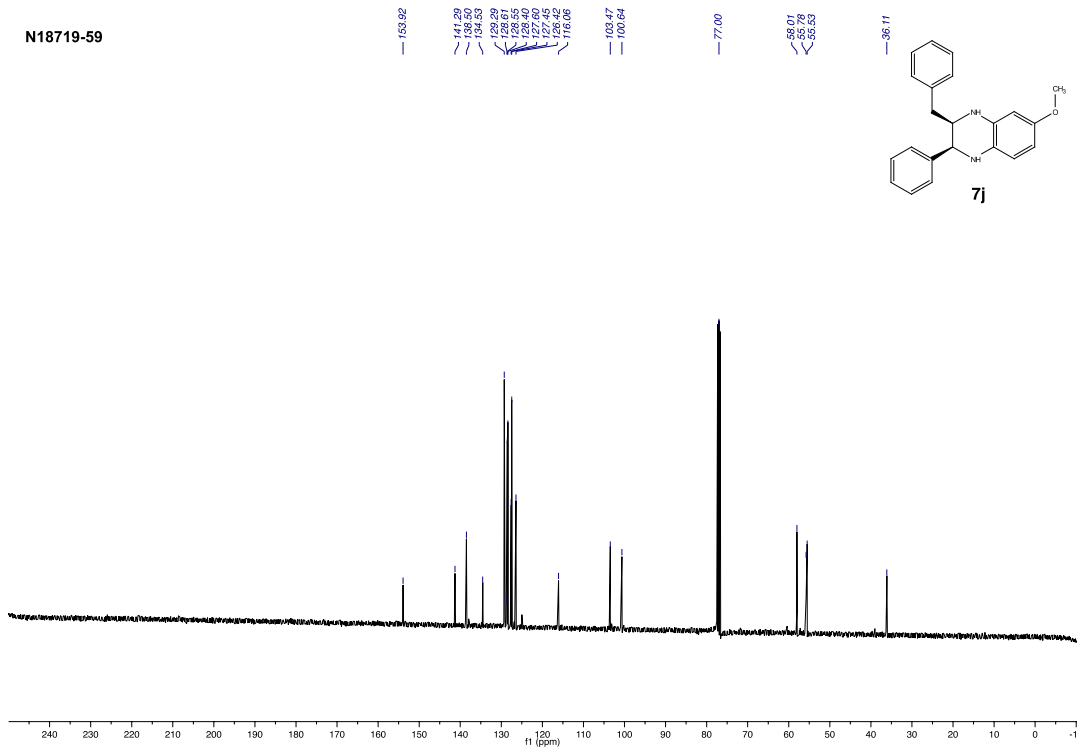
N19497-15-1



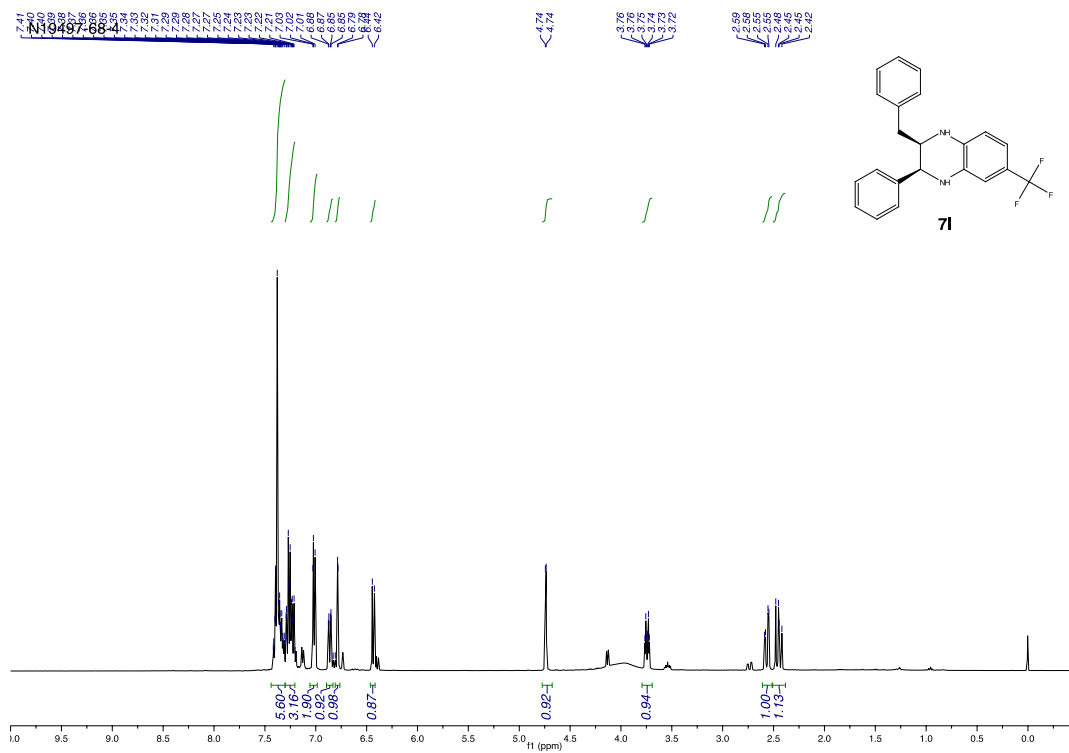
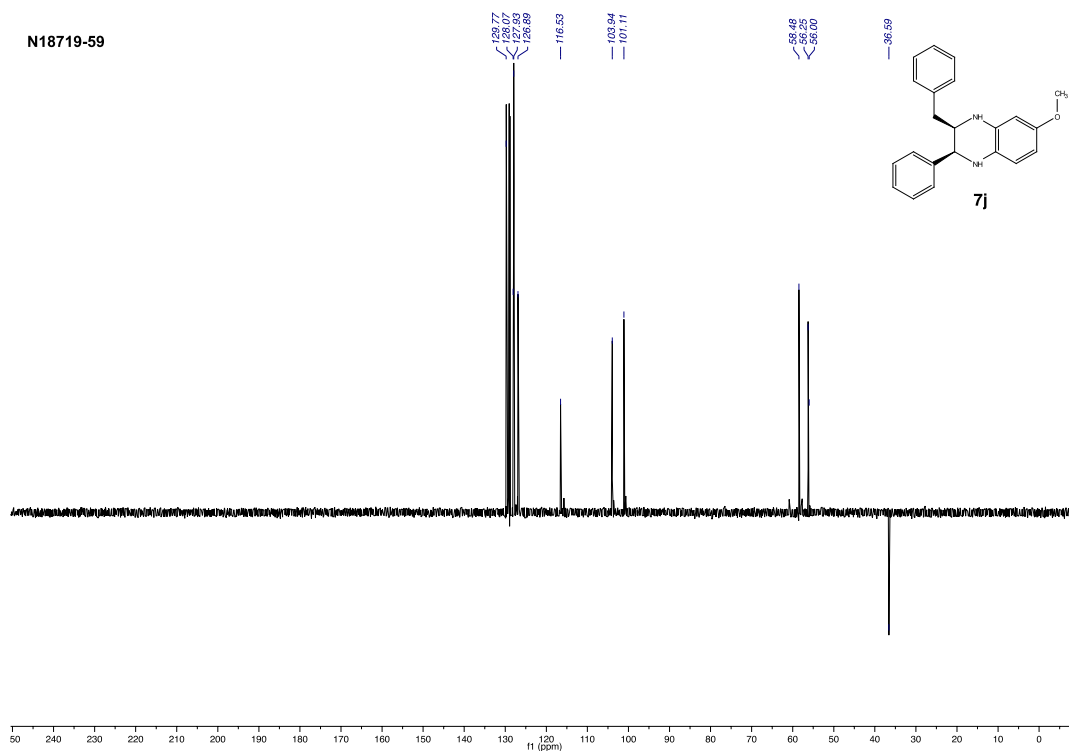
N18719-59



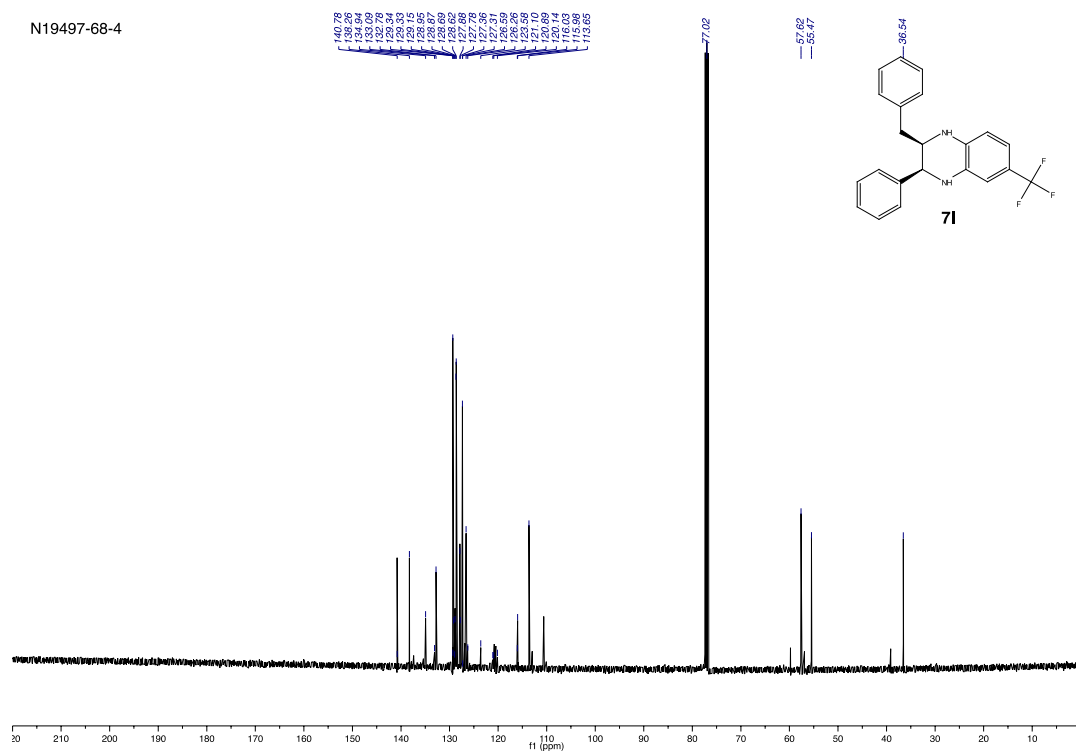
N18719-59



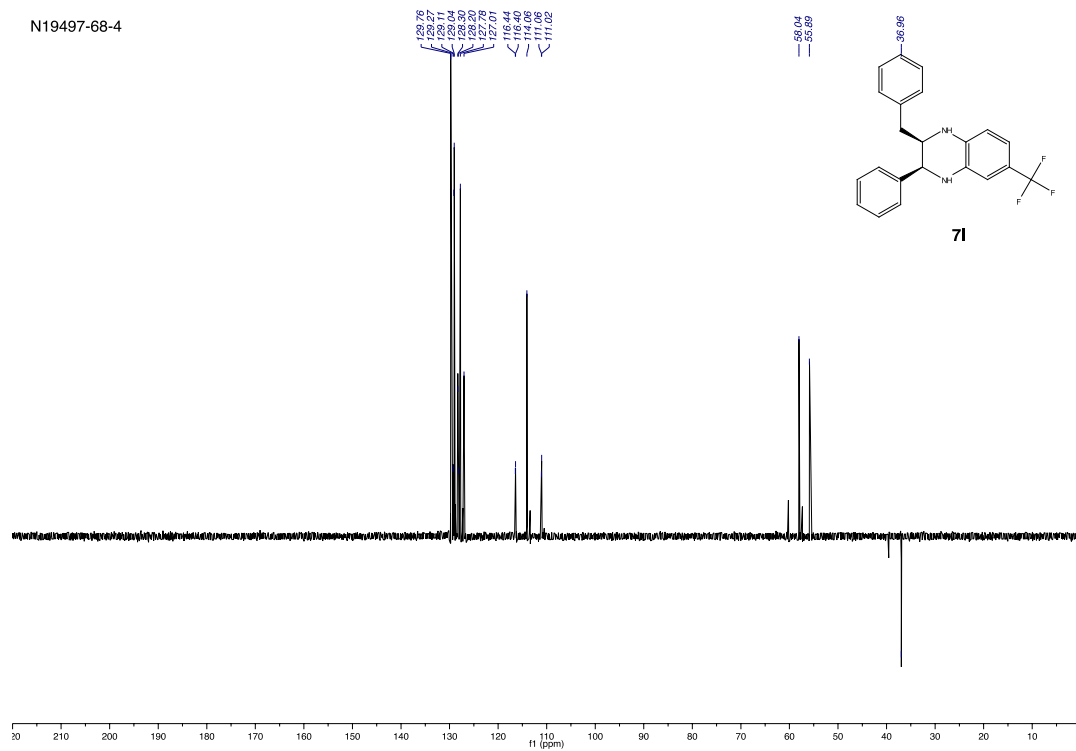
N18719-59



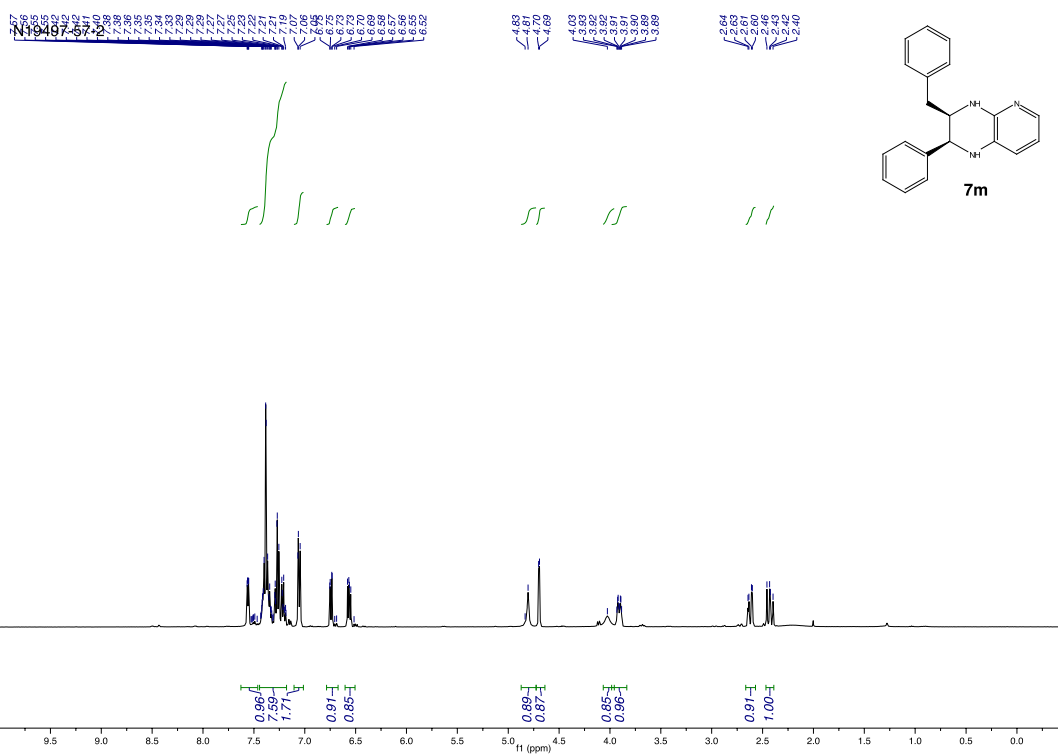
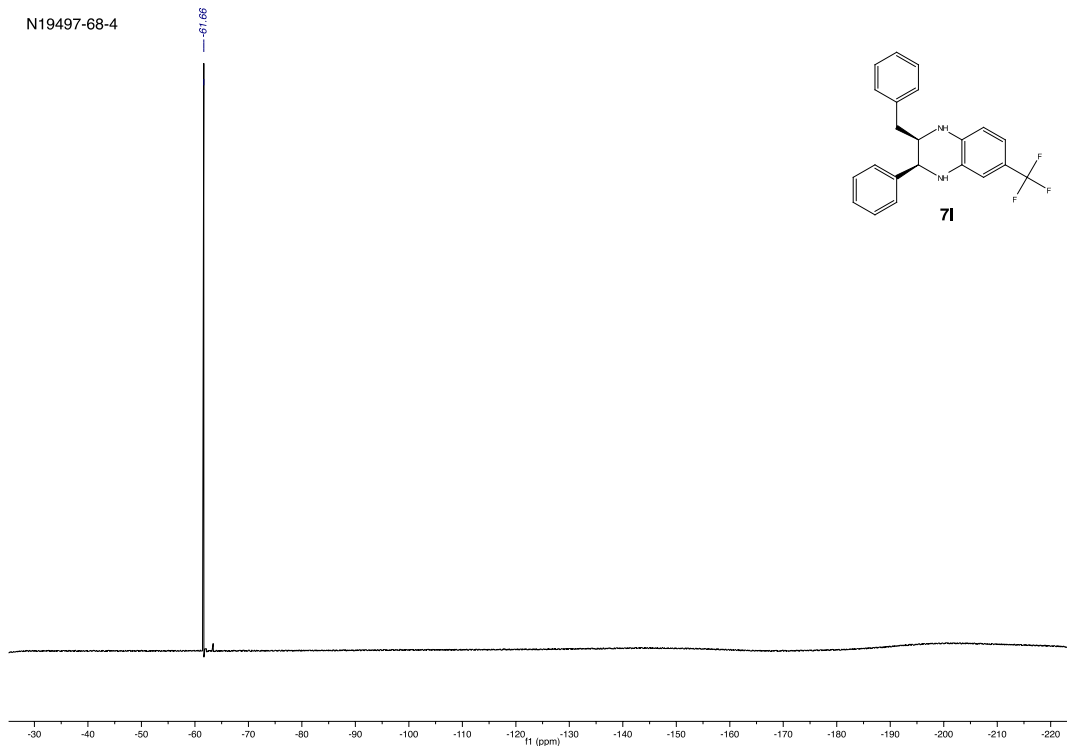
N19497-68-4



N19497-68-4



N19497-68-4

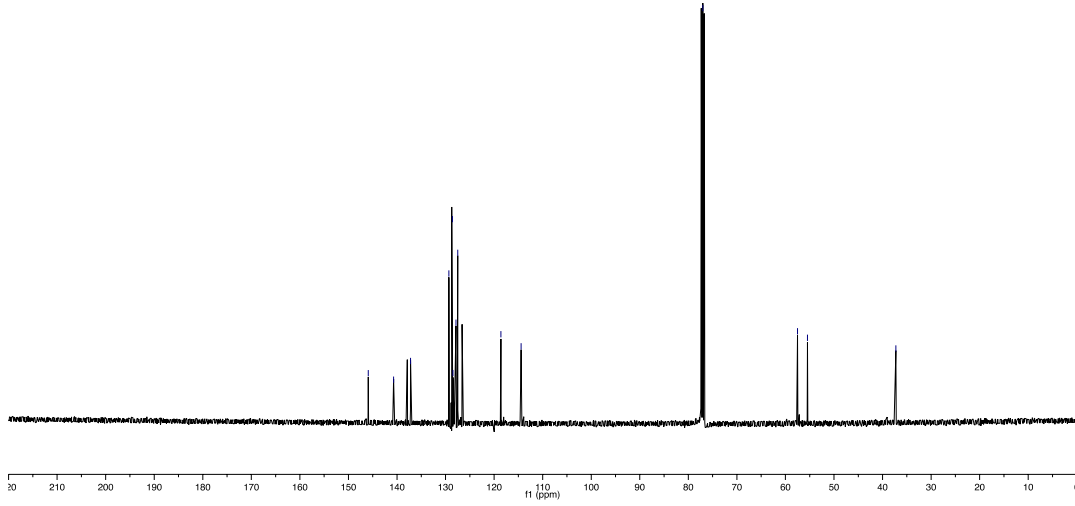
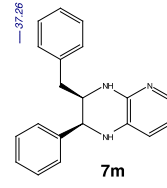


N19497-57-2

145.91
140.69
137.21
130.32
128.59
128.56
127.49
118.60
114.43

77.02

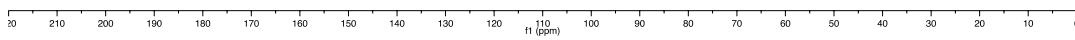
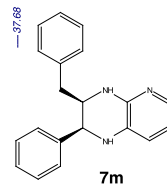
57.52
55.46

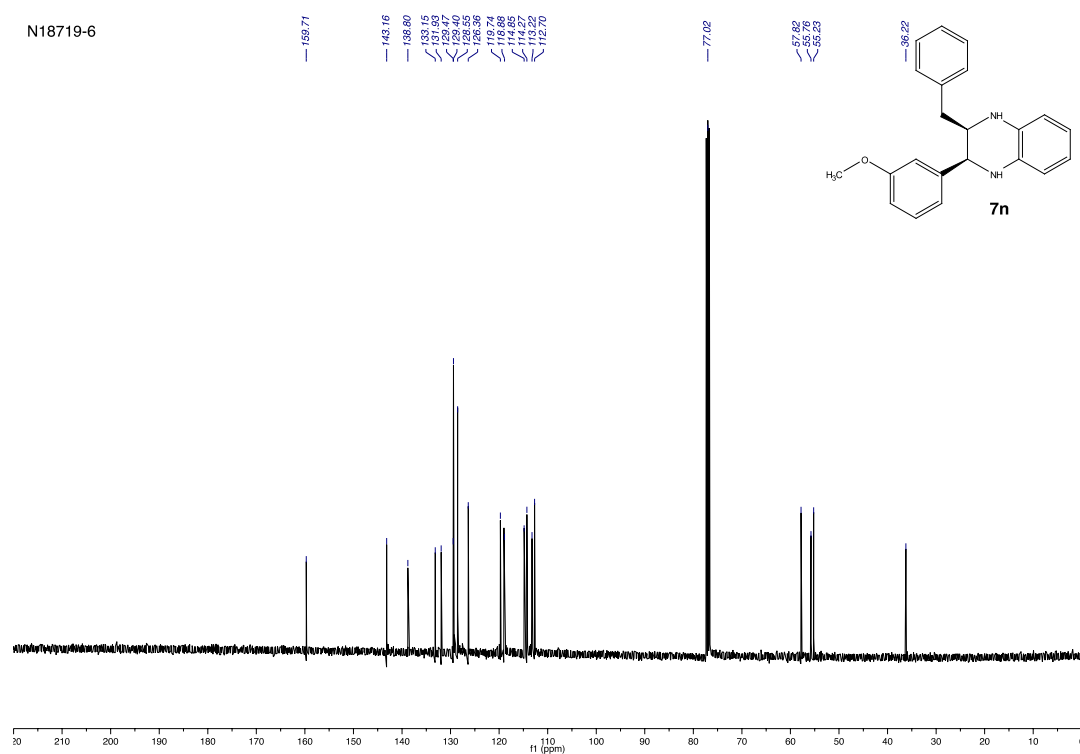
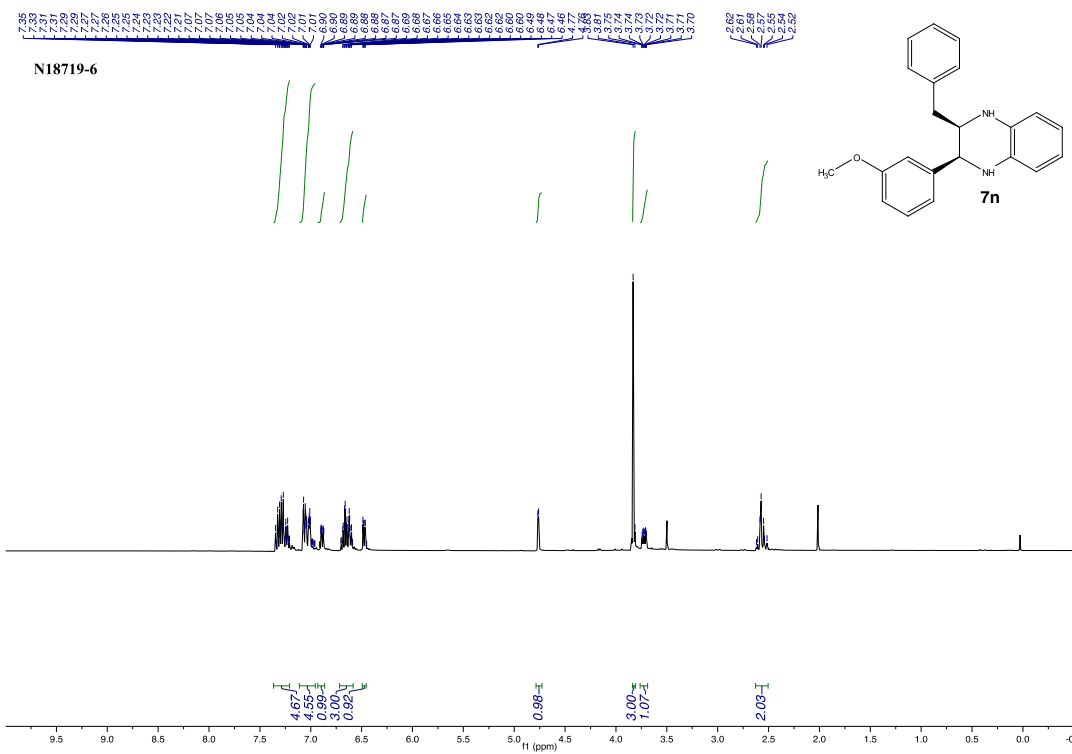


N19497-57-2

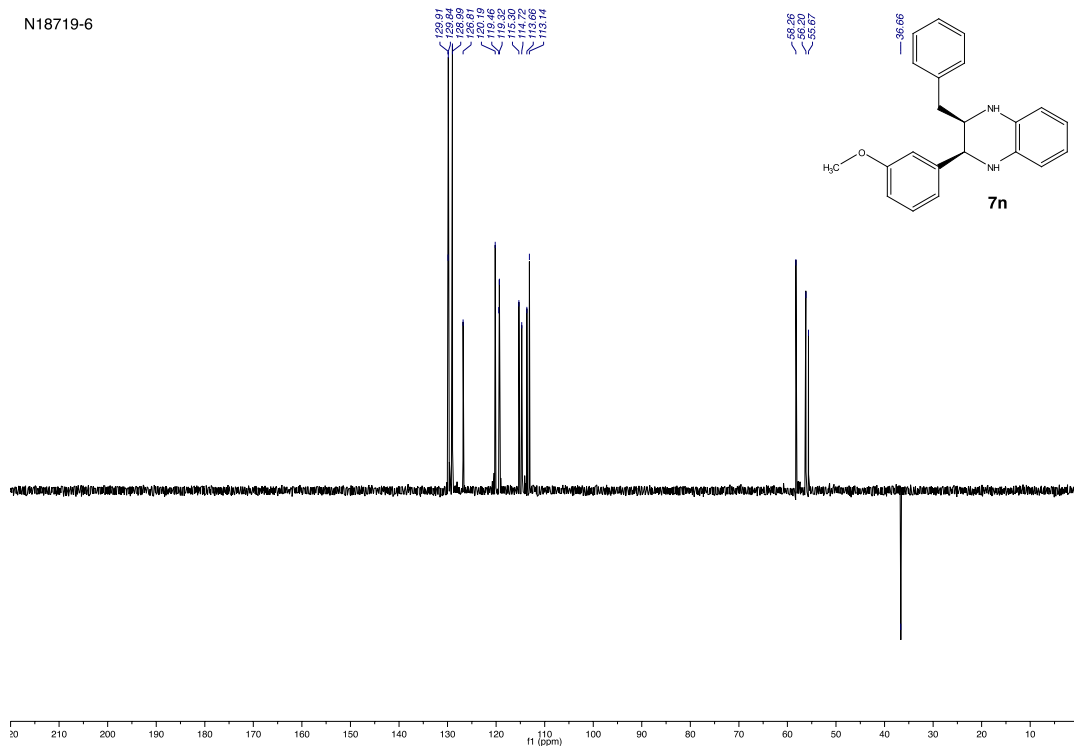
137.63
130.74
129.14
128.27
127.20
118.02
114.85

57.94
55.88

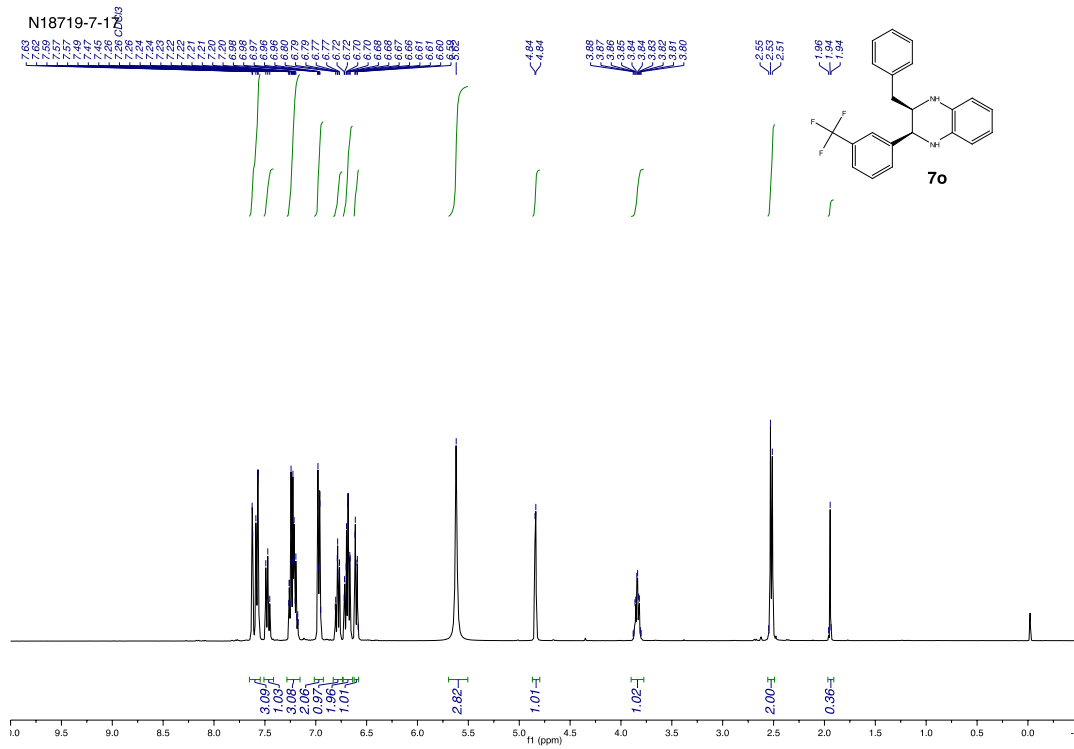




N18719-6



N18719-7-1

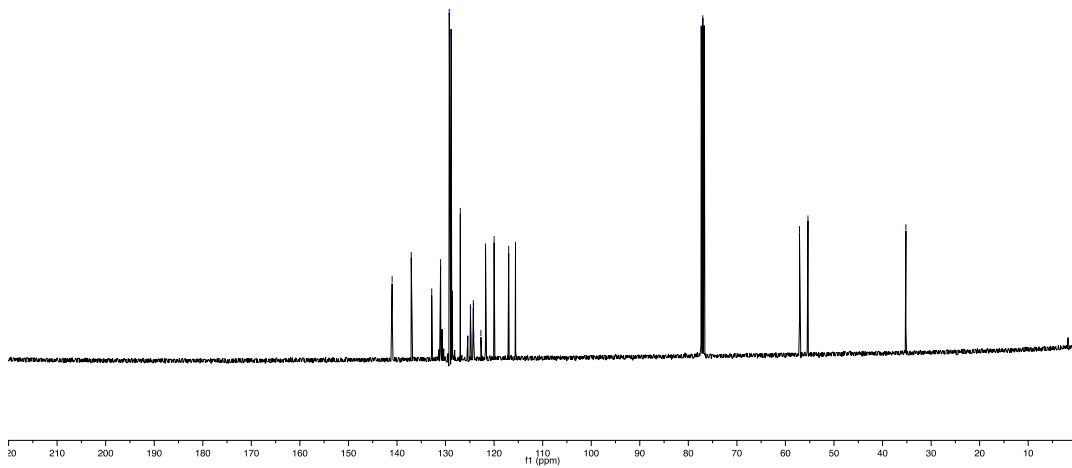
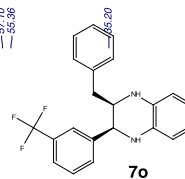


N18719-7-17

141.00
132.85
131.02
128.65
124.30
124.66
124.26
124.24
122.71
121.00
115.59

— 77.02

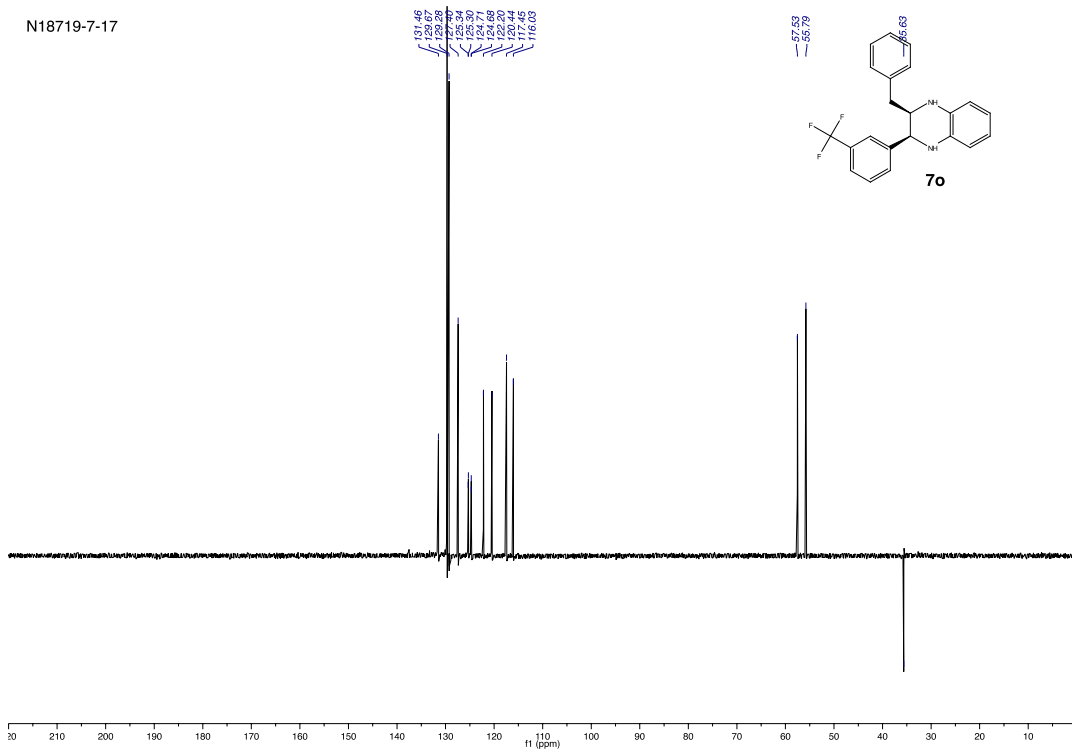
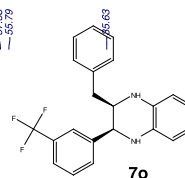
— 57.10
— 55.96



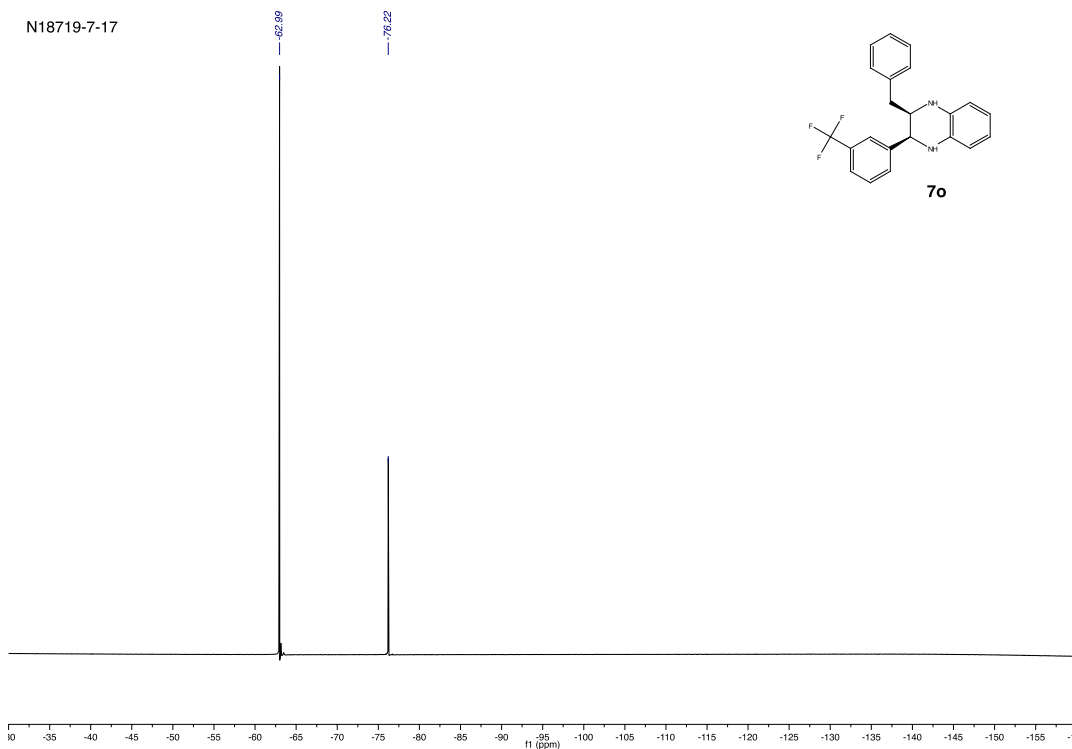
N18719-7-17

131.45
129.67
129.28
125.94
125.30
124.68
122.20
117.45
116.03

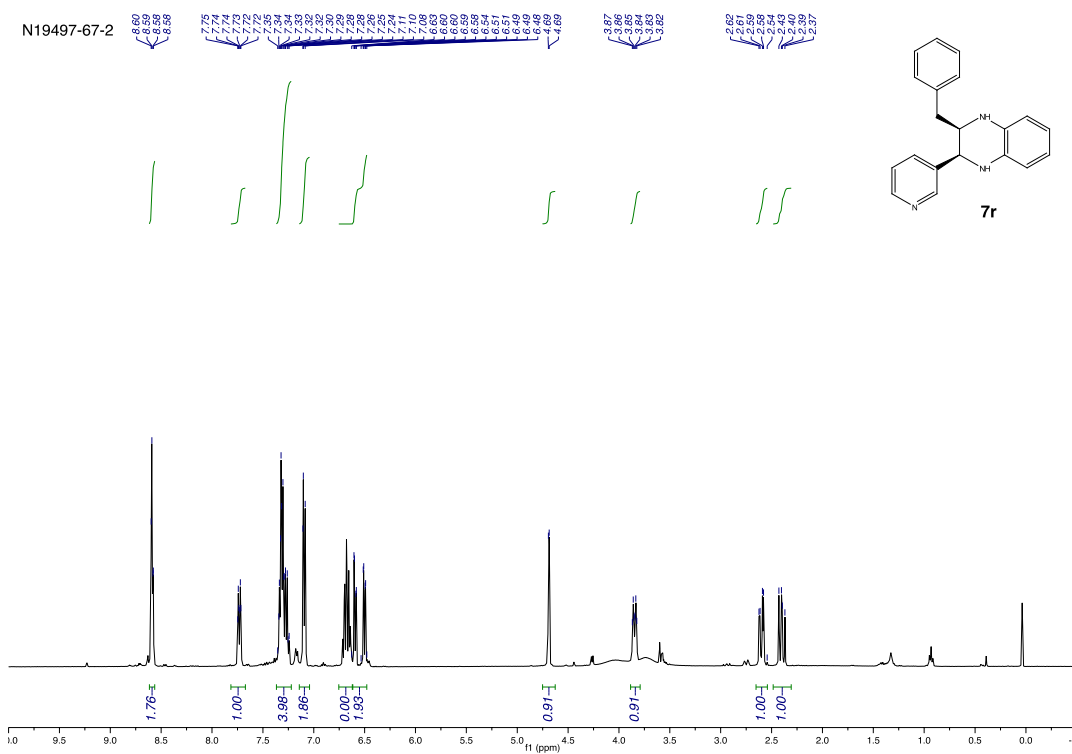
— 57.53
— 55.79



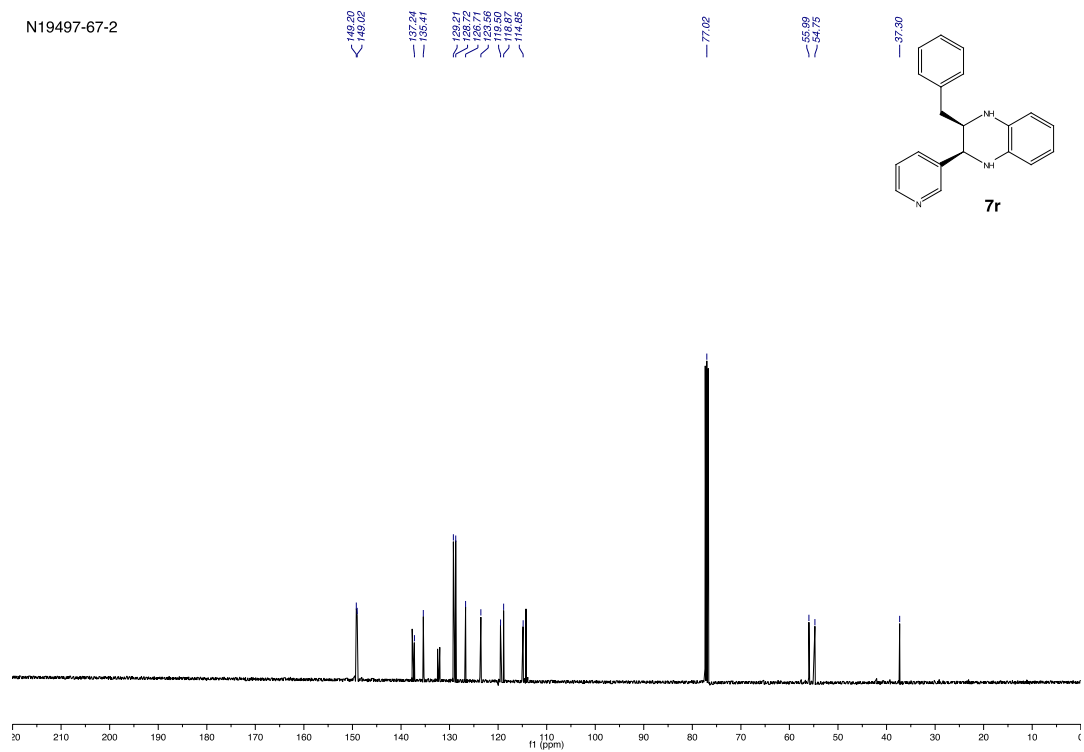
N18719-7-17



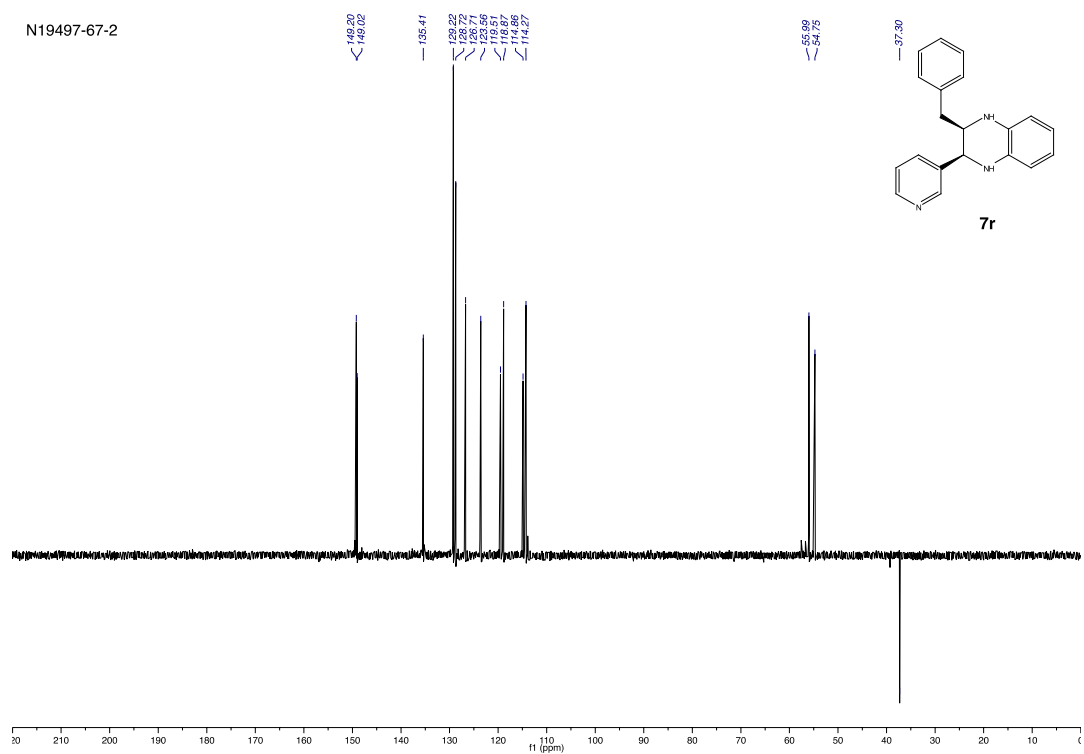
N19497-67-2

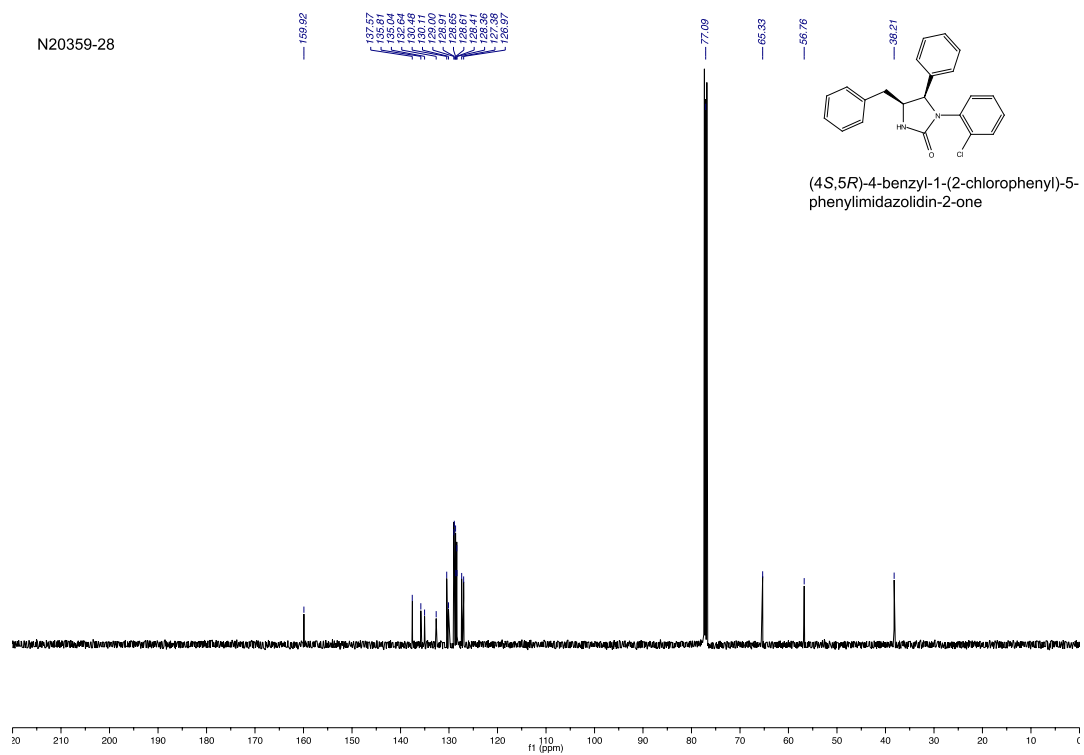
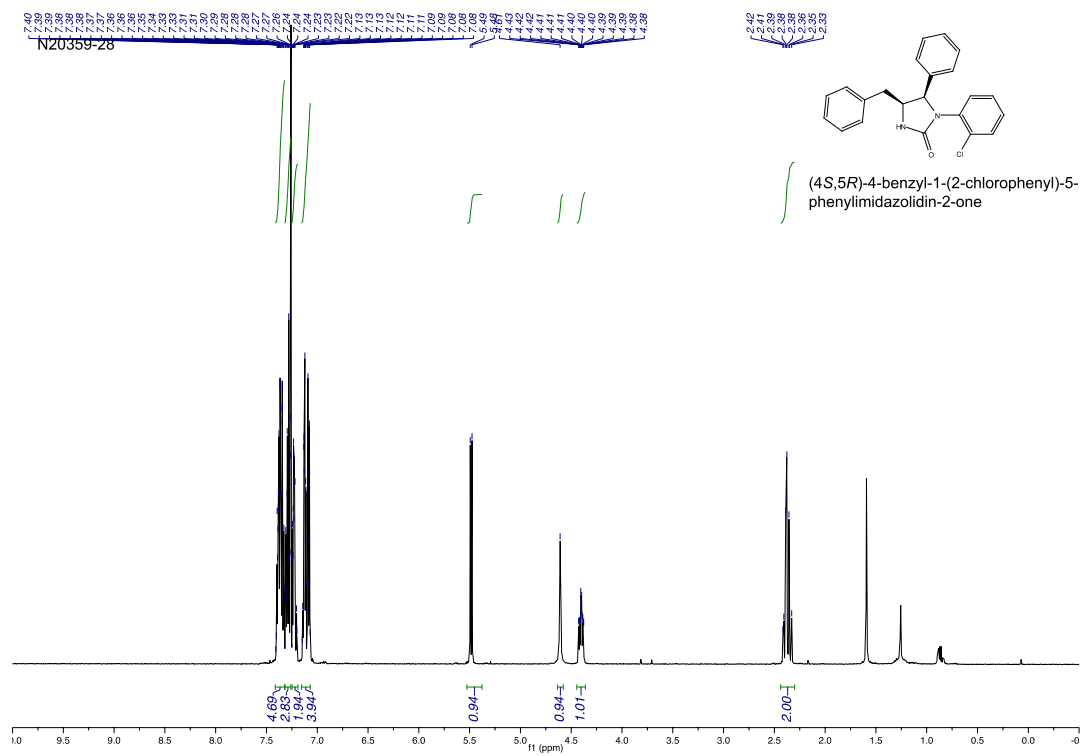


N19497-67-2



N19497-67-2





N20359-28

