

TiCl₄-*n*-Bu₃N-mediated cascade annulation of ketones with α -ketoesters: a facile synthesis of highly substituted fused γ -alkylidene butenolides

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^bAcademy of Scientific and Innovative Research (AcSIR), Ghaziabad 201002, India

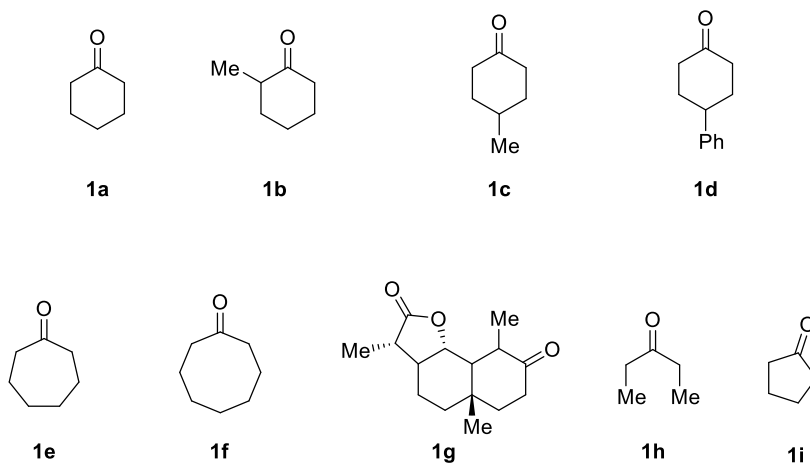
^cCenter for Materials Characterization, CSIR-National Chemical Laboratory, Dr. Homi Bhabha Road, Pune 411008, India

*E-mail: k.ravindar@ncl.res.in

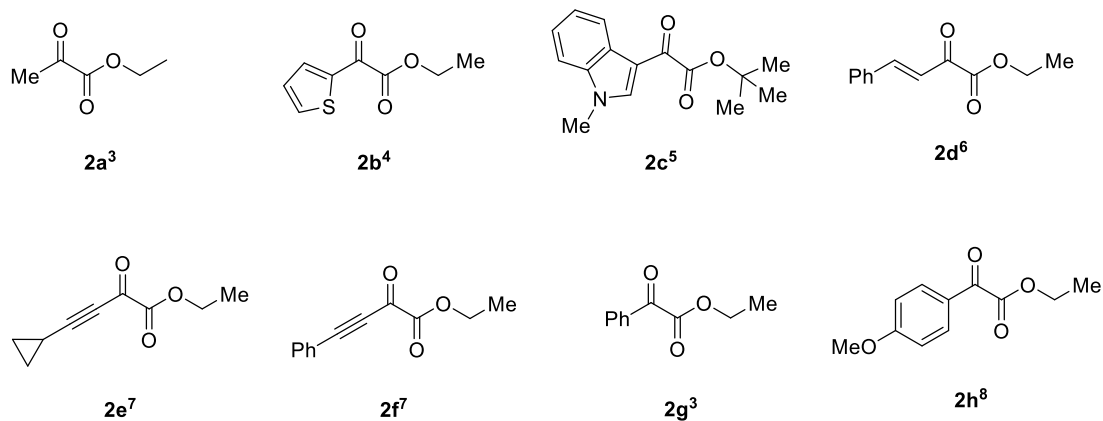
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1. Synthesis of ketones (1):^{1,2}



2. Synthesis of α -ketoesters (2): Prepared using reported procedures.^{3,4,5,6,7,8}



¹ 1a-1f, 1h and 1i were purchased from commercial sources.

²

³ 2a and 2g were purchased from commercial sources.

⁴ Meng, Q.; Sun, Y.; Vidal, V. R.; Gene't, J. P.; Zhang, Z. *J. Org. Chem.* **2008**, *73*, 3842-3847.

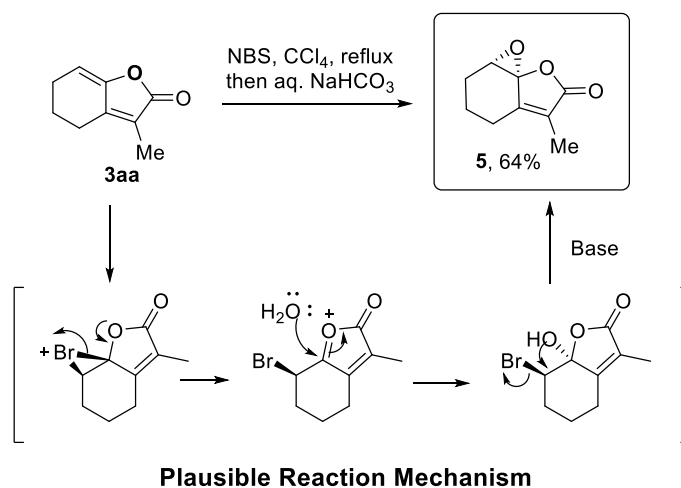
⁵ Hameury, T.; Guillemont, J.; Hijfte, L. V.; Bellosta, V.; Cossy, J. *Org. Lett.*, **2009**, *11*, 2397-2400.

⁶ Dujardin, G.; Leconte, S.; Benard, A.; Brown, E. *Synlett*, **2001**, *1*, 147-149.

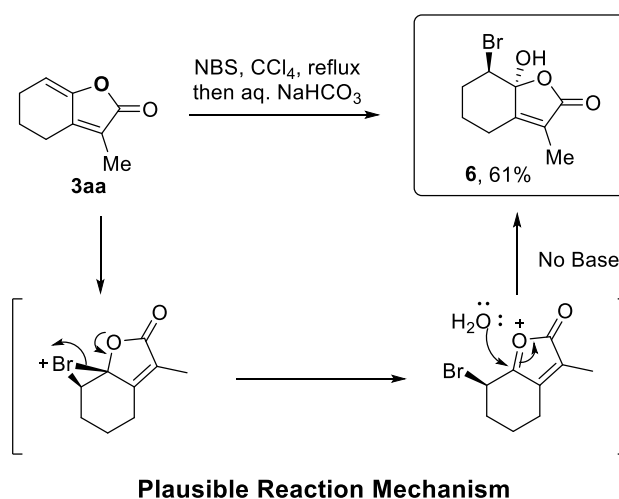
⁷ (2e & 2f), Sinha, D.; Biswas, A.; Singh, V. K. *Org. Lett.* **2015**, *17*, 3302-3305.

⁸ Kambale, D. A.; Thorat, S. S.; Pratapure, M. S.; Gonnade, R. G.; Kontham, R. *Chem. Commun.*, **2017**, *53*, 6641-6644.

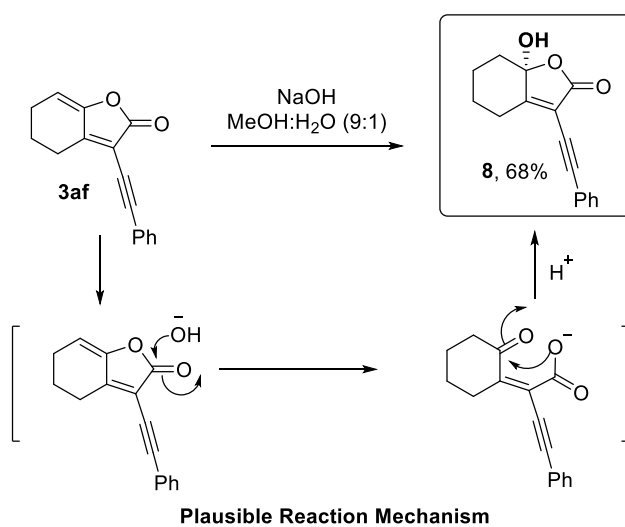
3. Plausible reaction mechanism for the synthesis of 5:



Plausible reaction mechanism for the synthesis of 6:

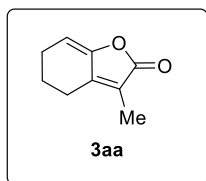


Plausible reaction mechanism for the synthesis of 8:

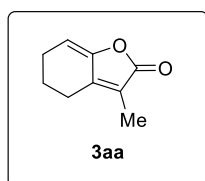
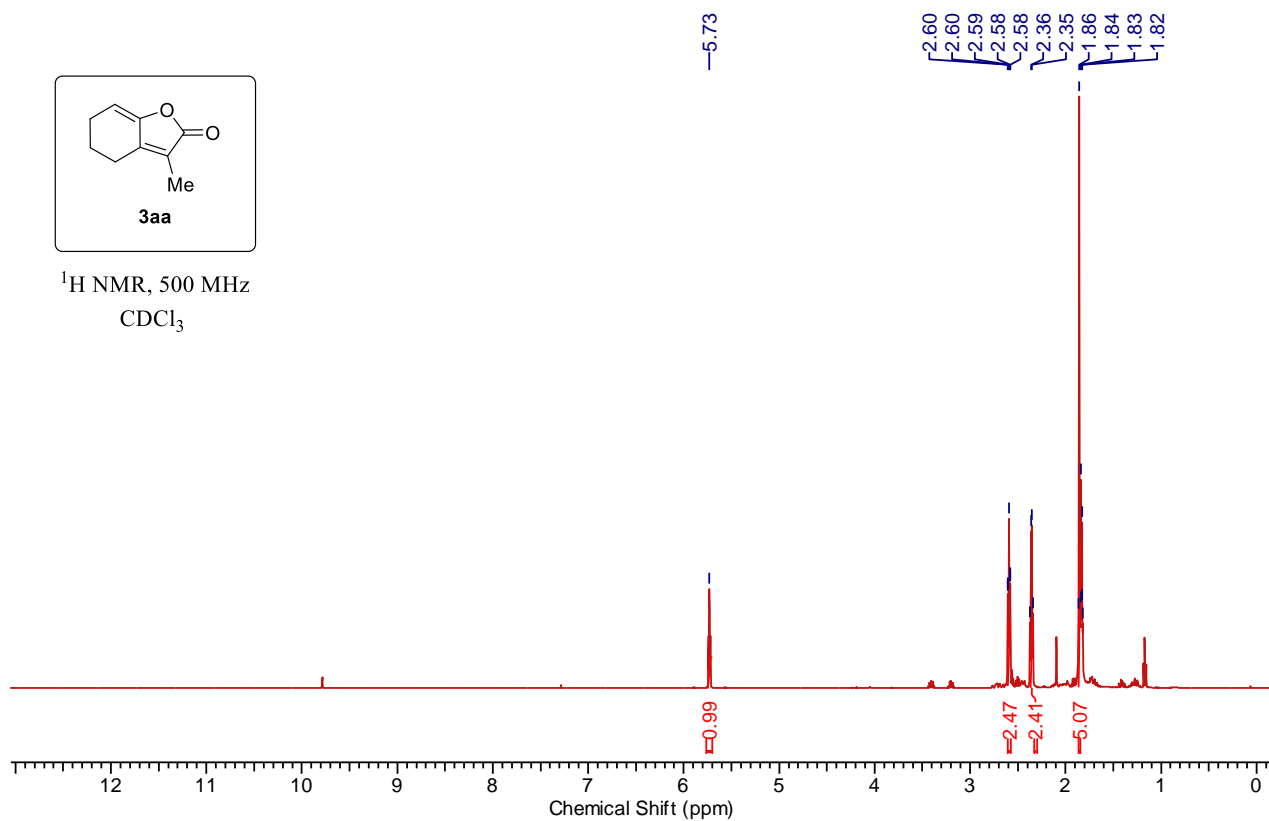


4. ^1H , ^{13}C NMR, DEPT and 2D NMR Spectra

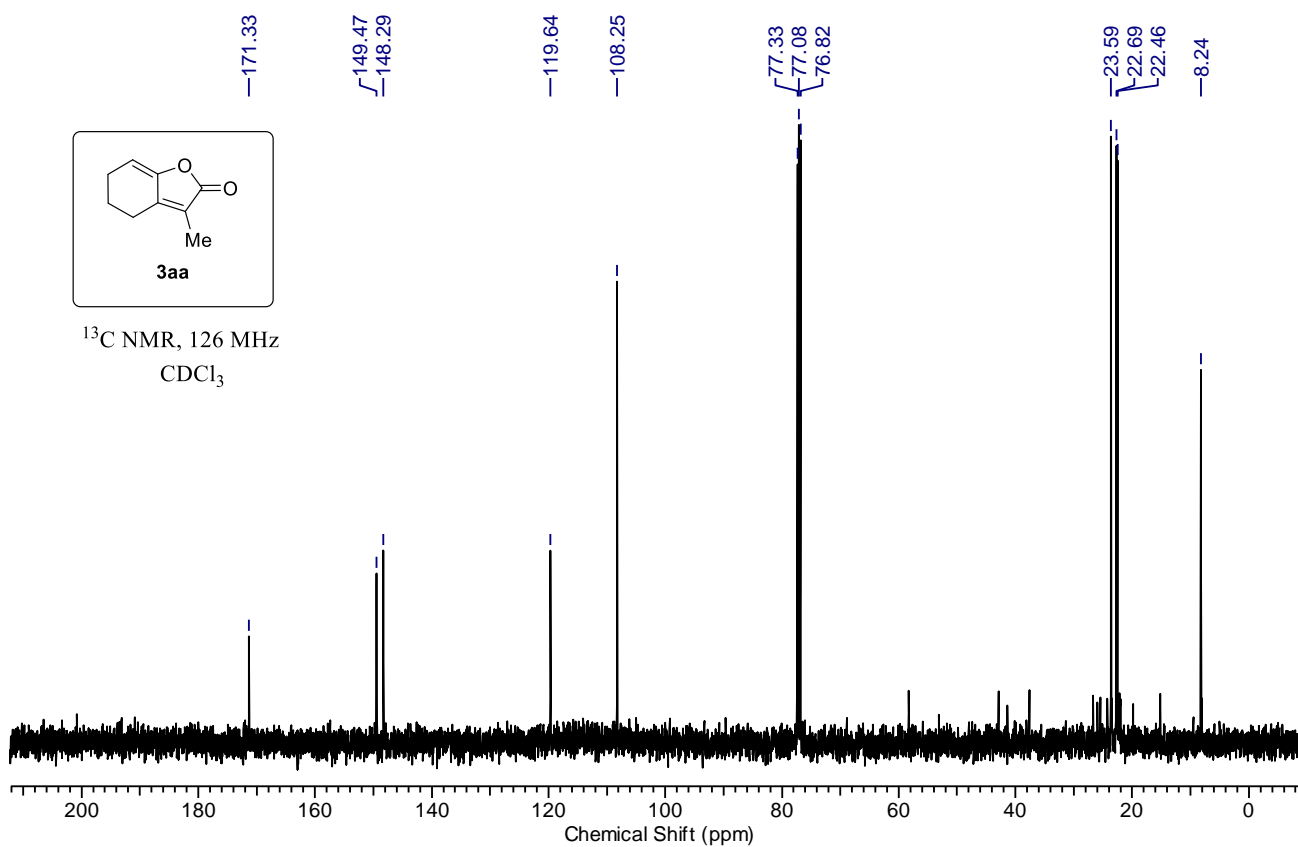
3-Methyl 5, 6-dihydrobenzofuran-2(4H)-one (3aa):



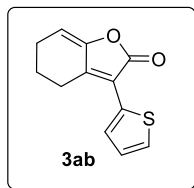
^1H NMR, 500 MHz
 CDCl_3



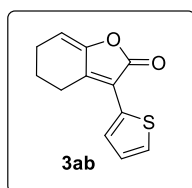
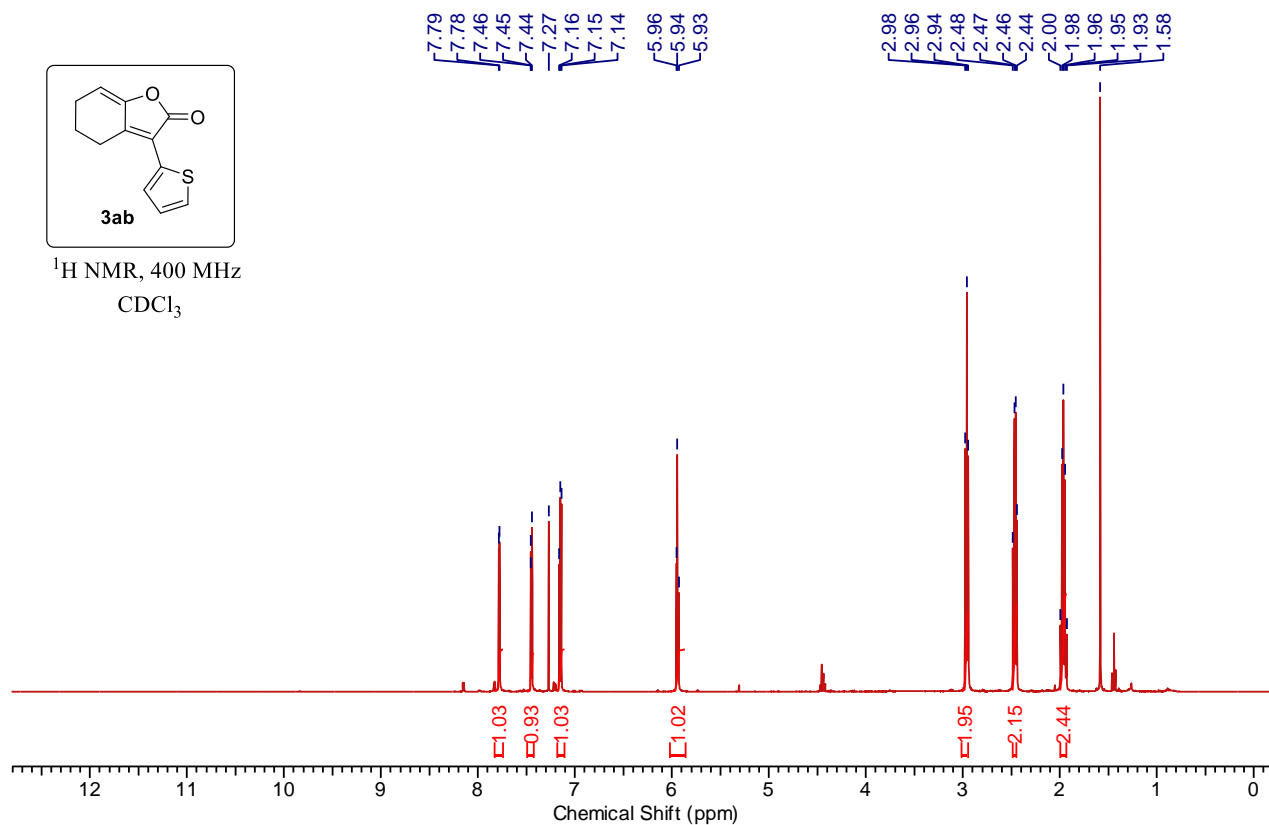
^{13}C NMR, 126 MHz
 CDCl_3



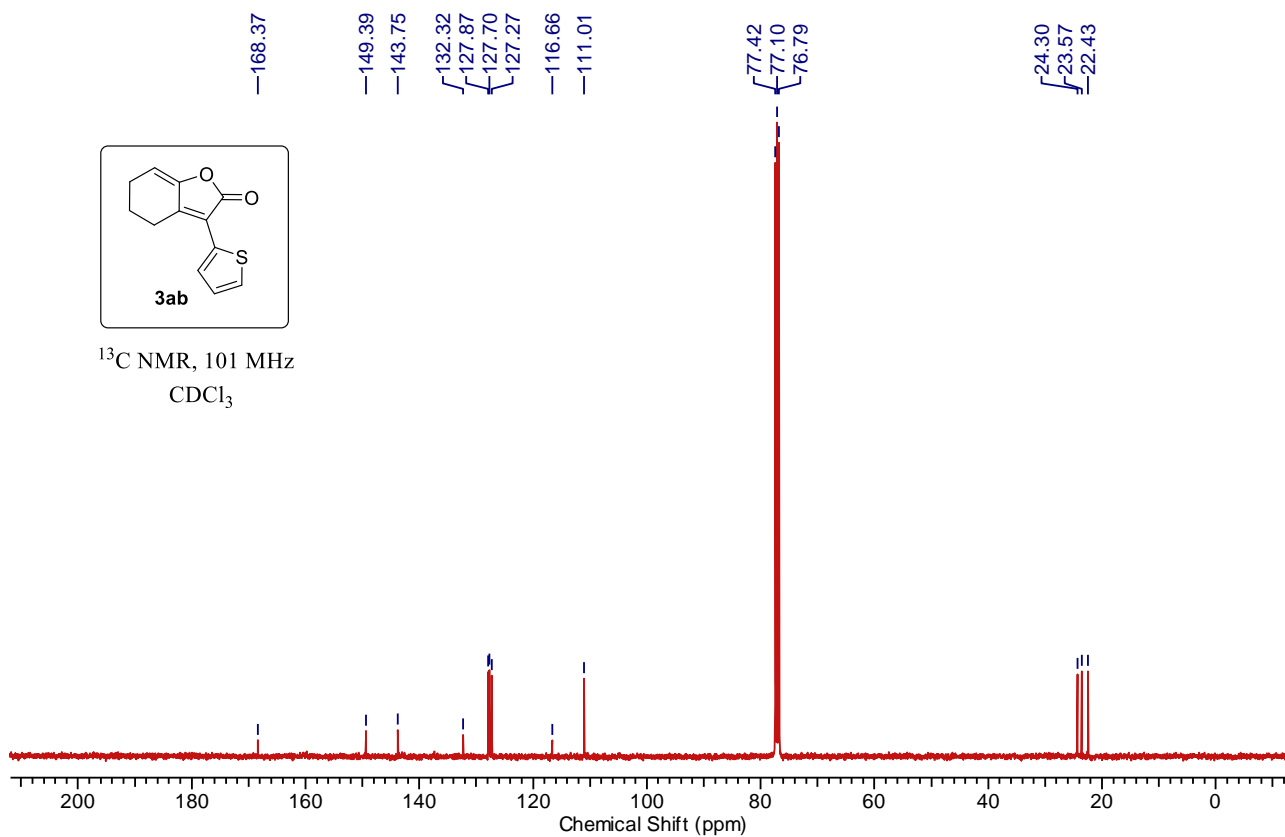
3-(Thiophen-2-yl)-5,6-dihydrobenzofuran-2(4H)-one (3ab):



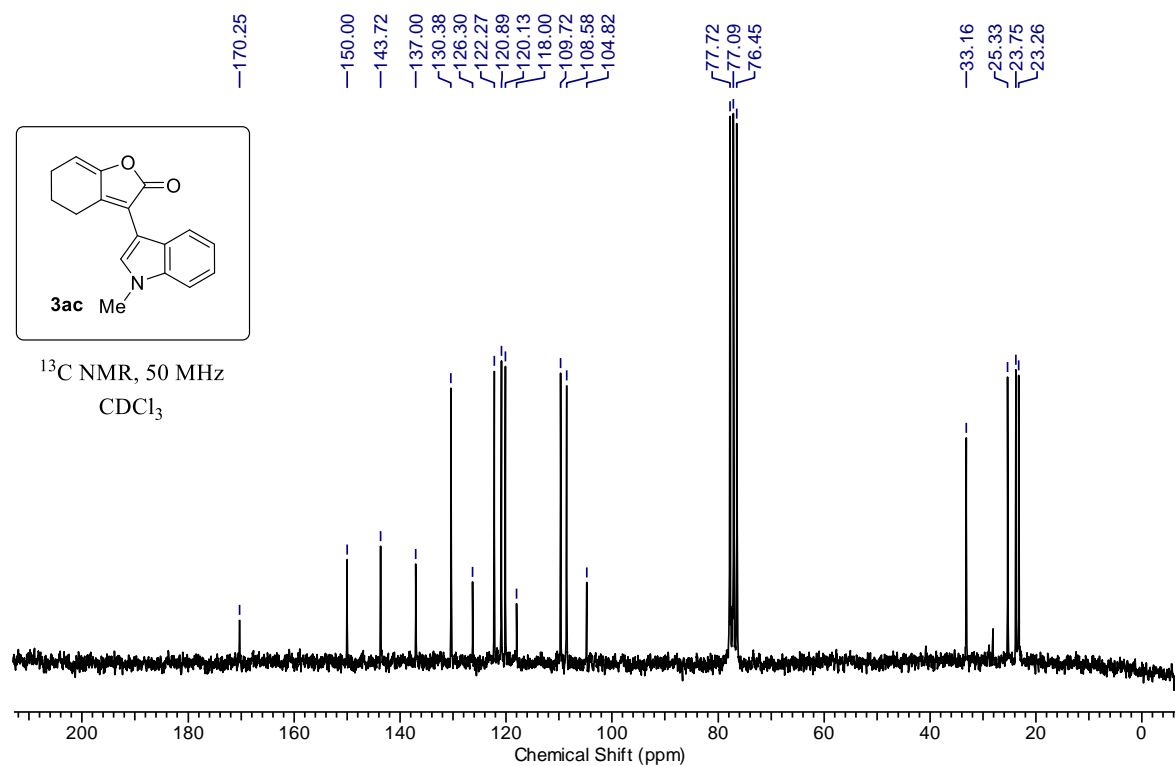
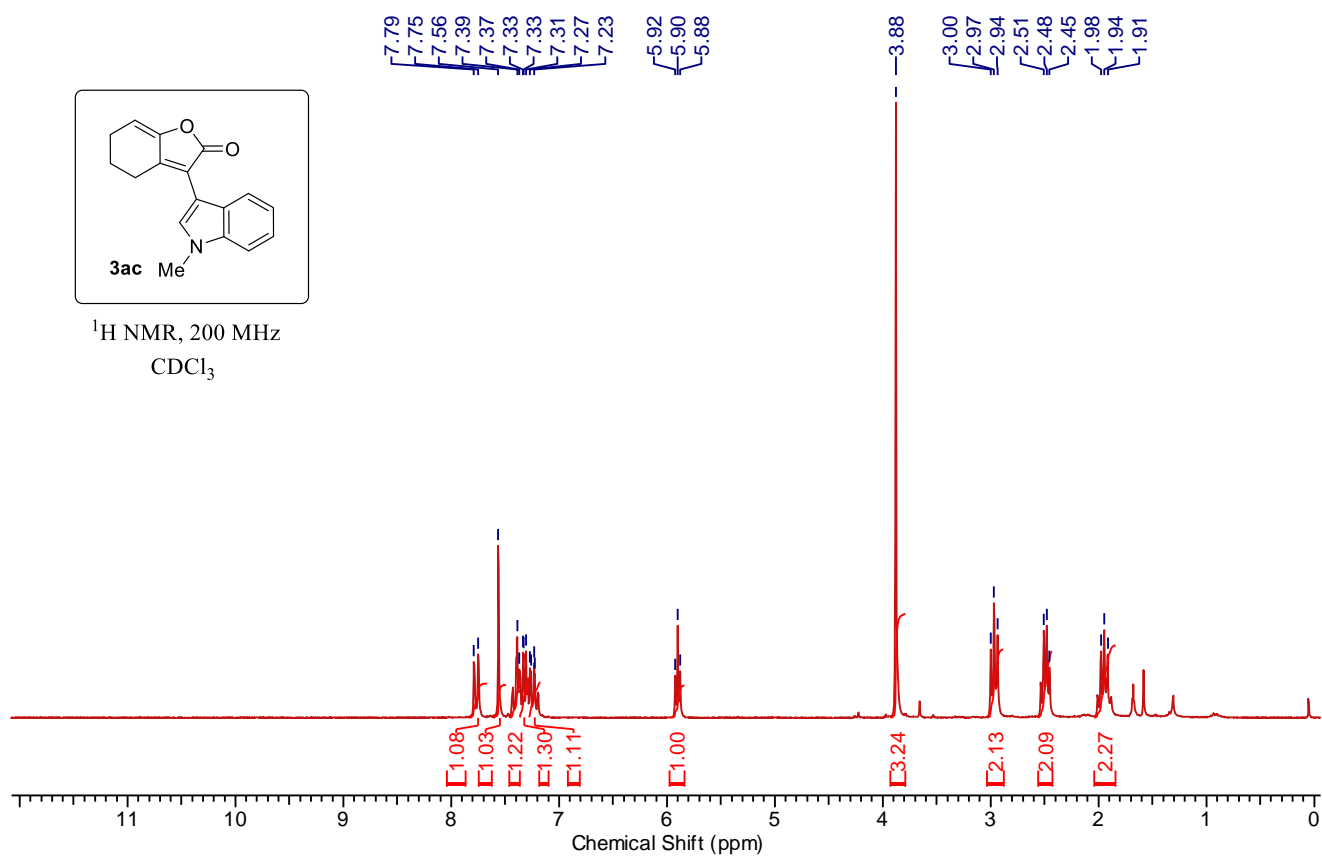
$^1\text{H NMR}$, 400 MHz
 CDCl_3



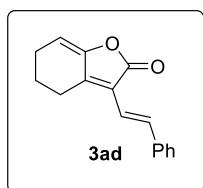
$^{13}\text{C NMR}$, 101 MHz
 CDCl_3



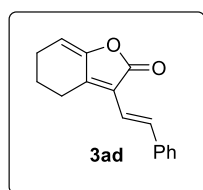
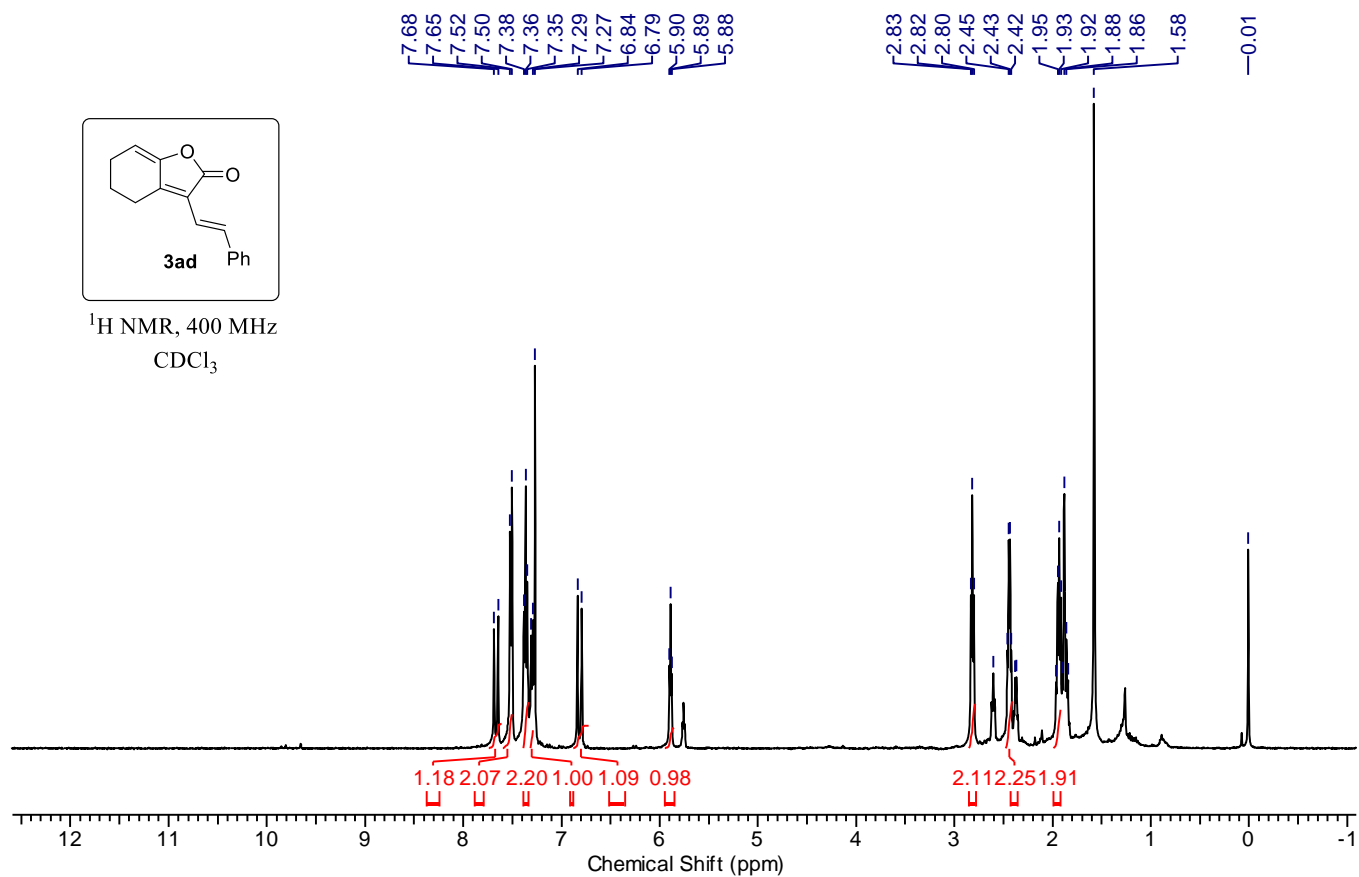
3-(1-Methyl-1*H*-indol-3-yl)-5,6-dihydrobenzofuran-2(4*H*)-one (3ac):



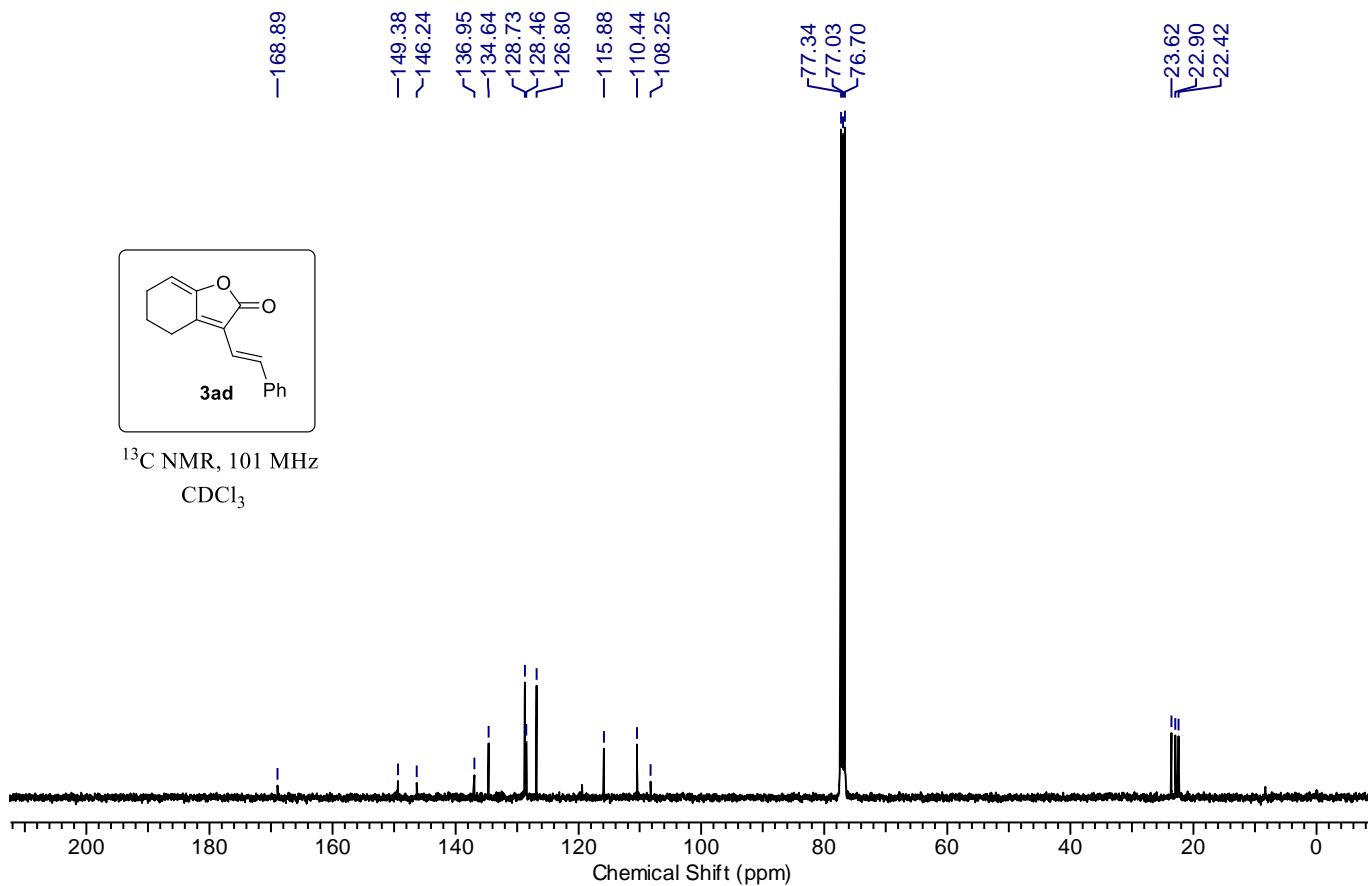
(E)-3-Styryl-5,6-dihydrobenzofuran-(2H)-one (3ad):



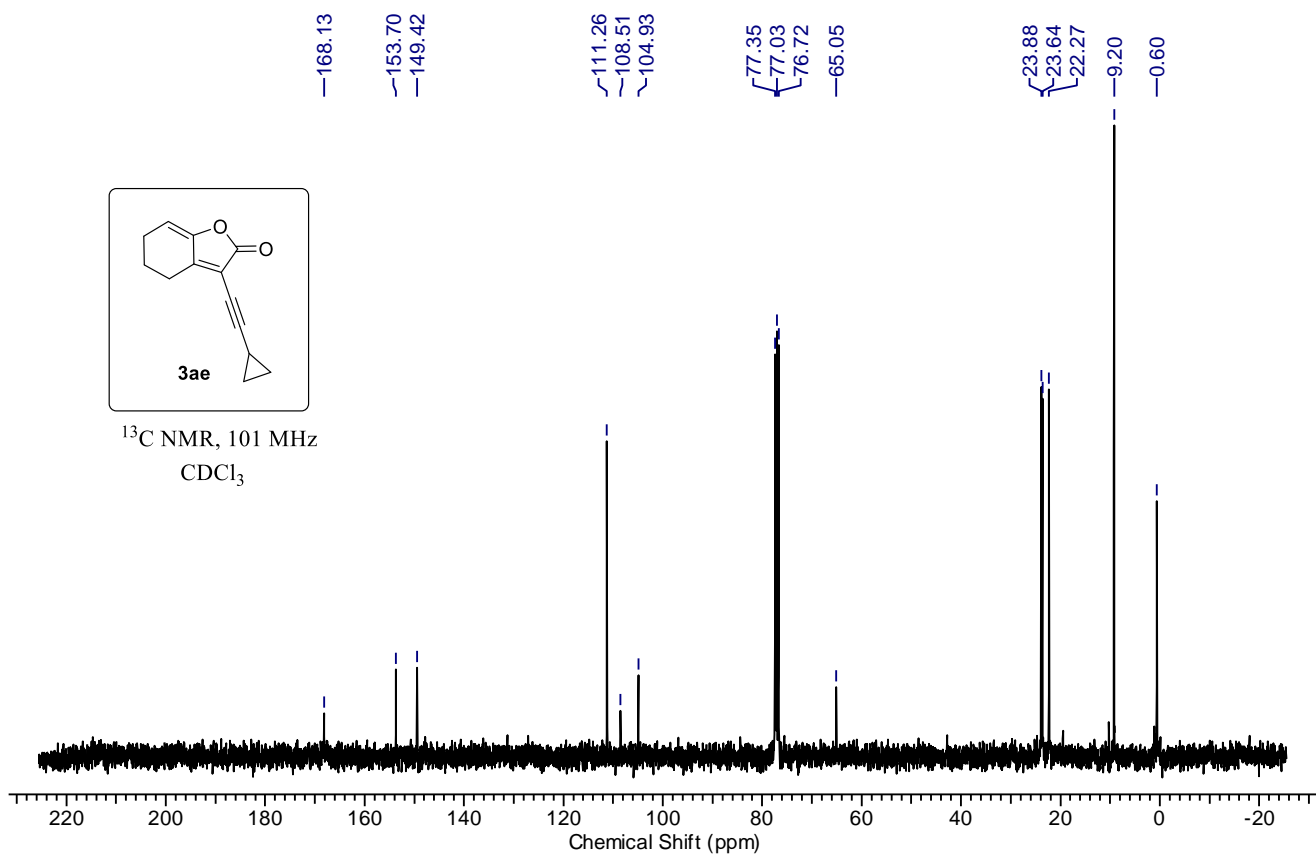
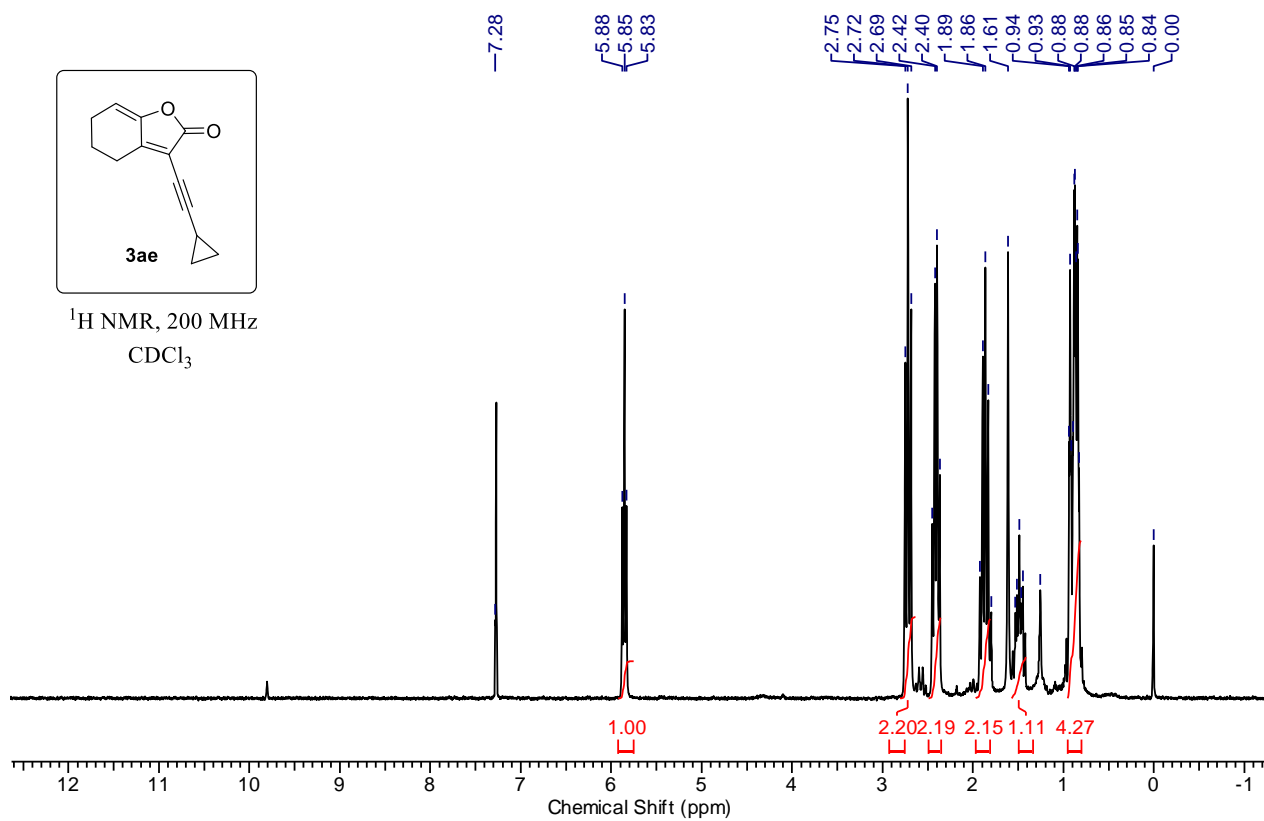
¹H NMR, 400 MHz
CDCl₃



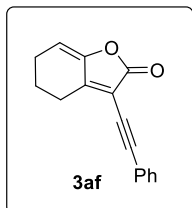
¹³C NMR, 101 MHz
CDCl₃



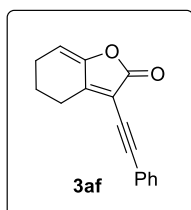
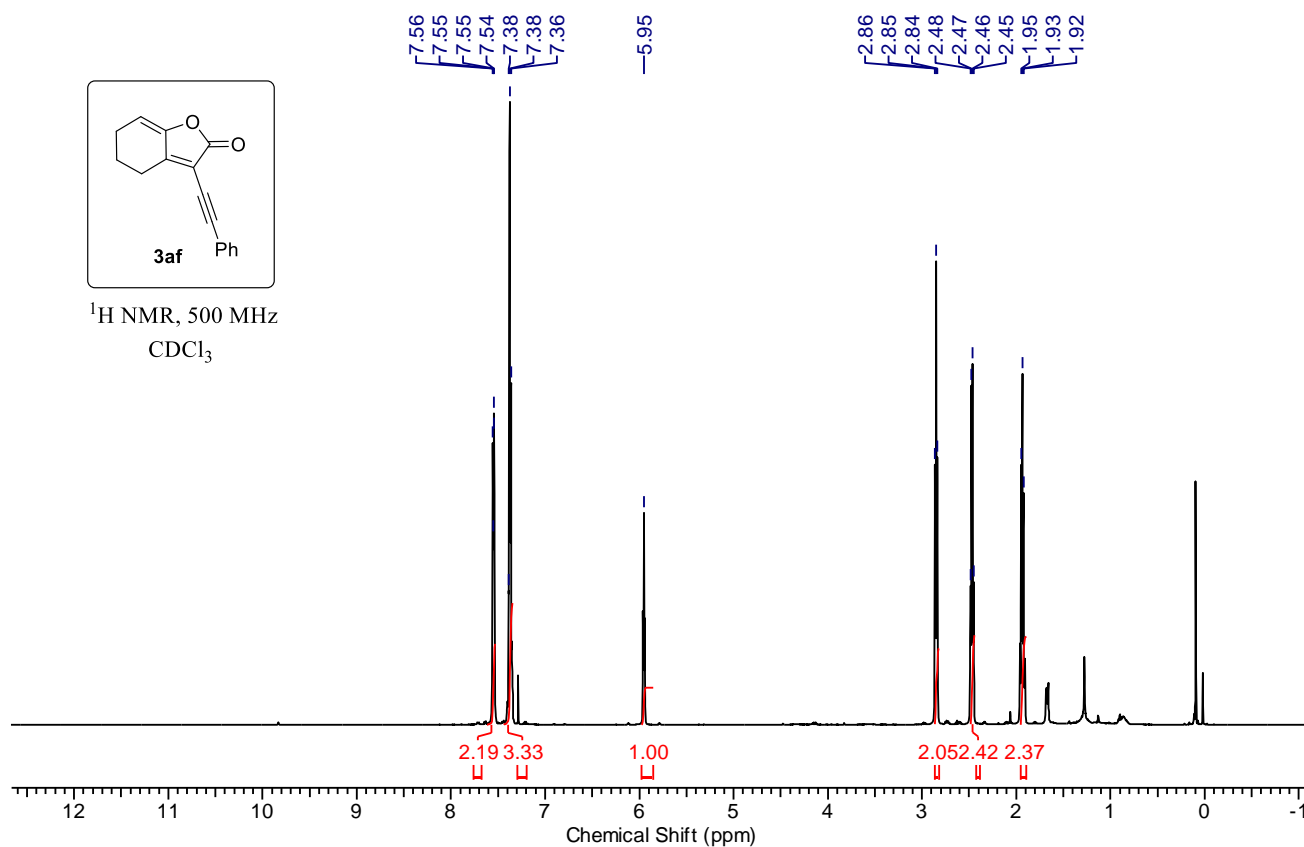
3-(Cyclopropylethynyl)-5,6-dihydrobenzofuran-2(4H)-one (3ae):



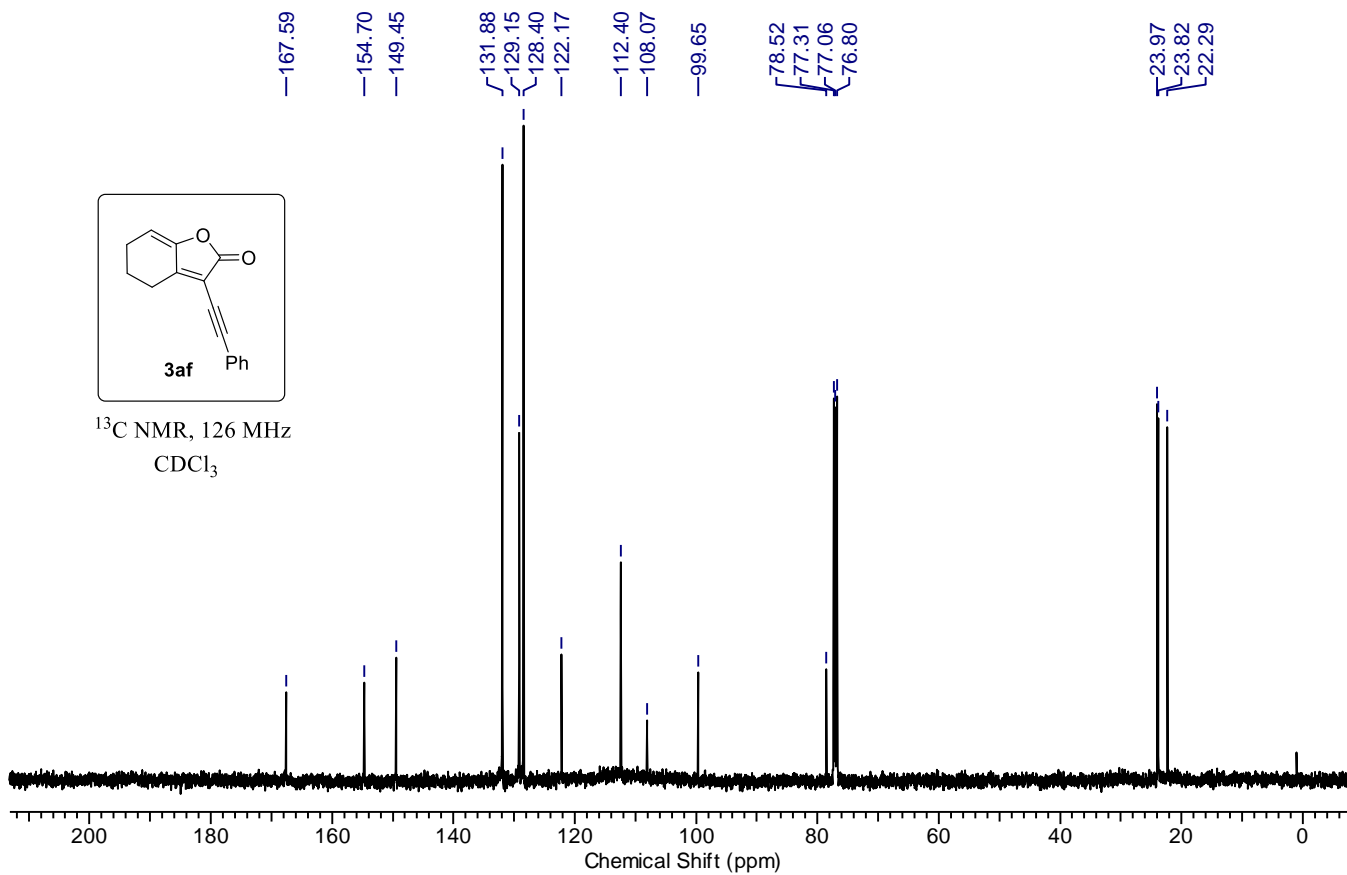
3-(Phenylethynyl)-5,6-dihydrobenzofuran-2(4H)-one (3af):



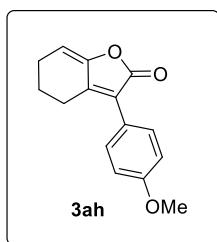
^1H NMR, 500 MHz
 CDCl_3



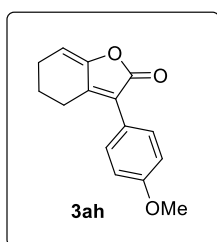
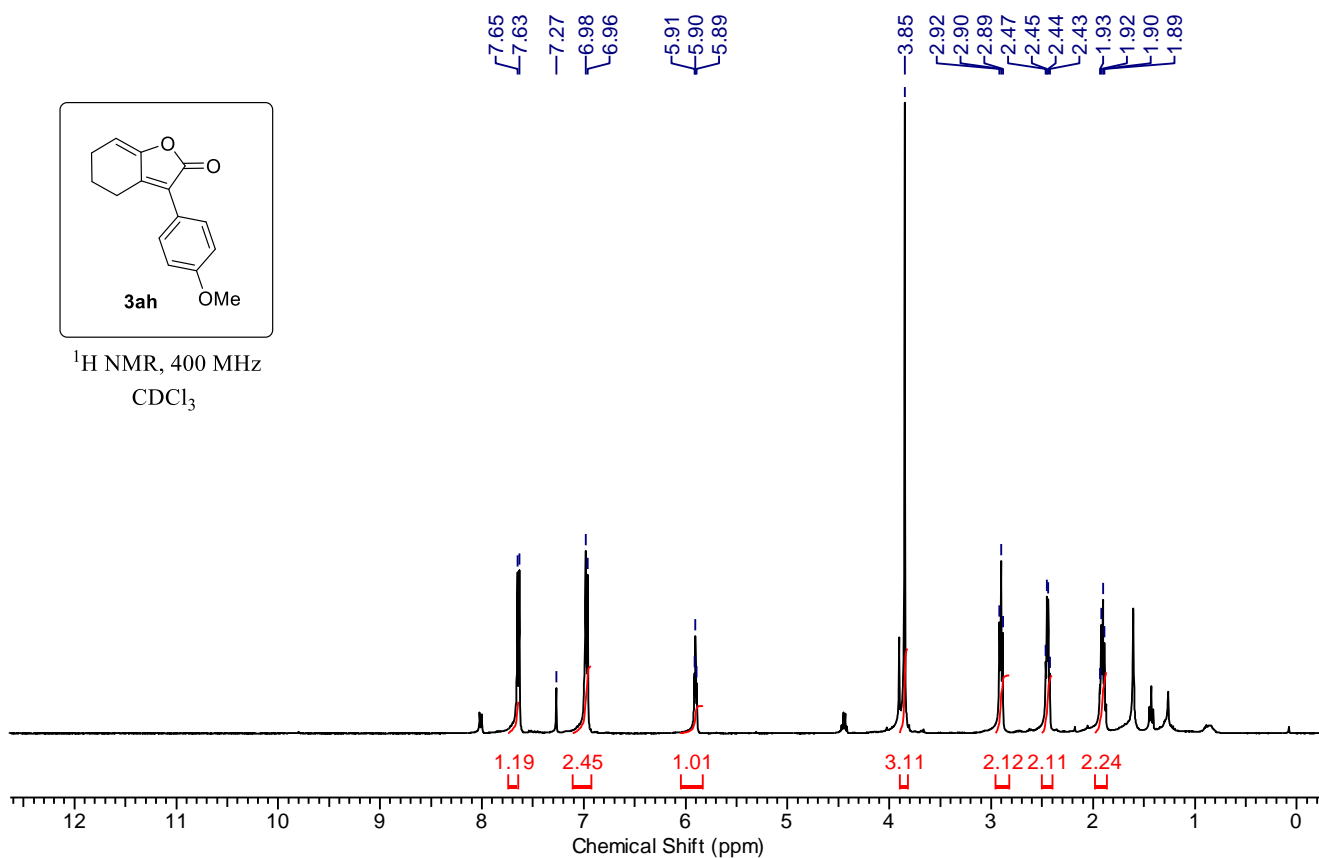
^{13}C NMR, 126 MHz
 CDCl_3



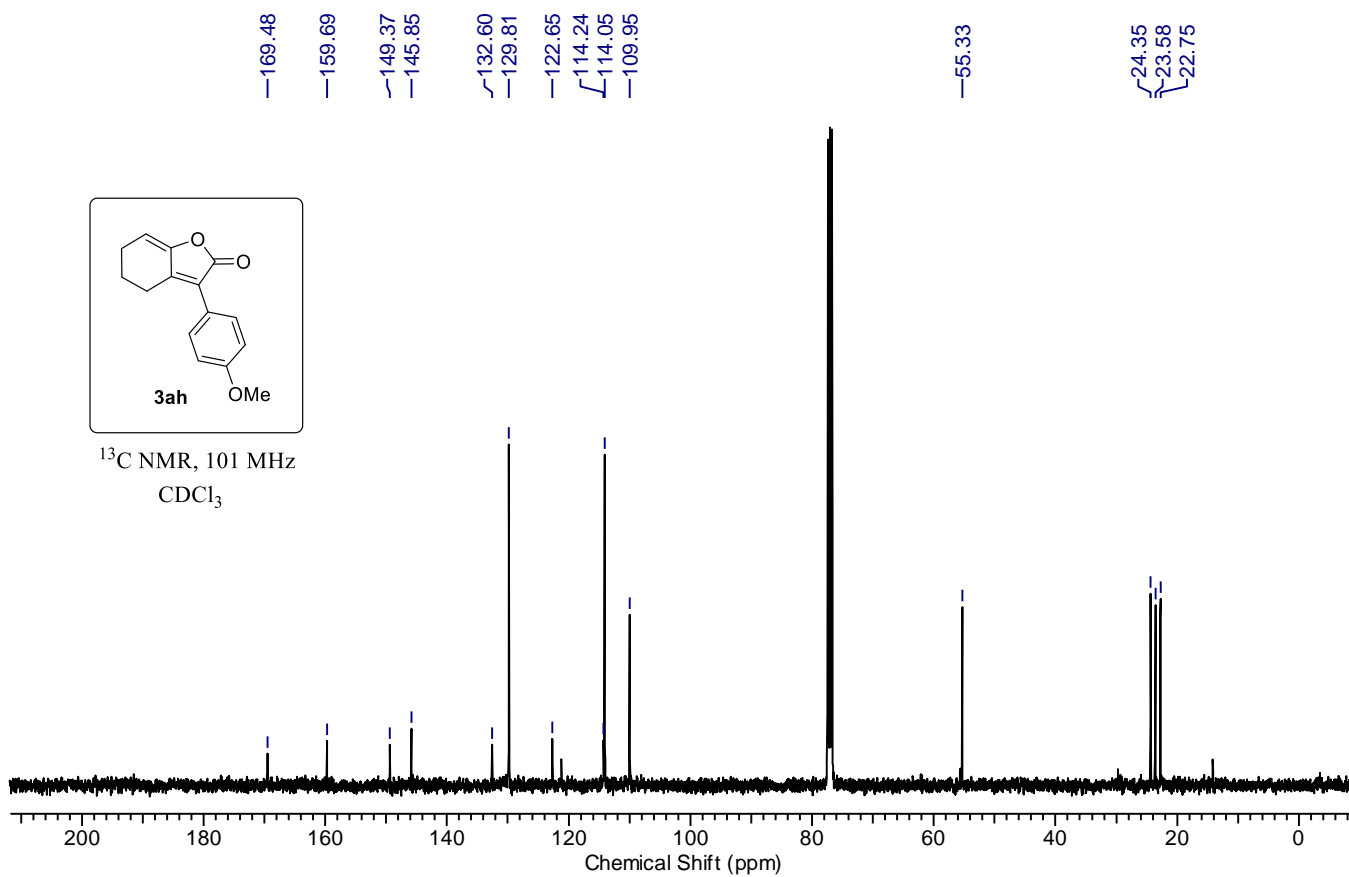
3-(4-Methoxyphenyl)-5,6-dihydrobenzofuran-(2H)-one (3ah):



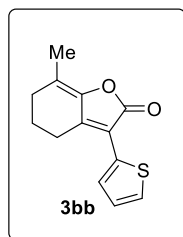
$^1\text{H NMR}$, 400 MHz
 CDCl_3



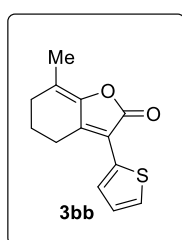
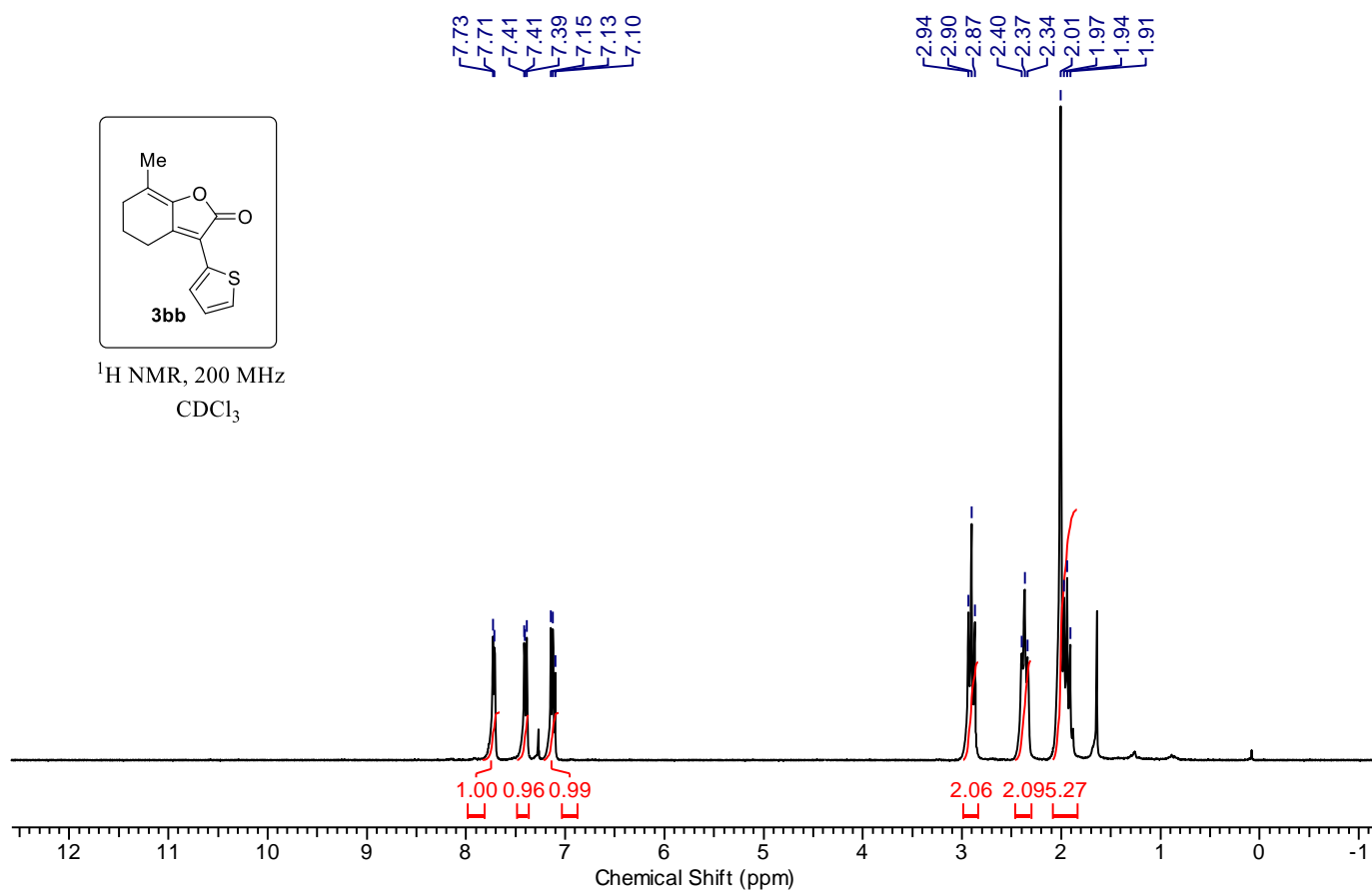
$^{13}\text{C NMR}$, 101 MHz
 CDCl_3



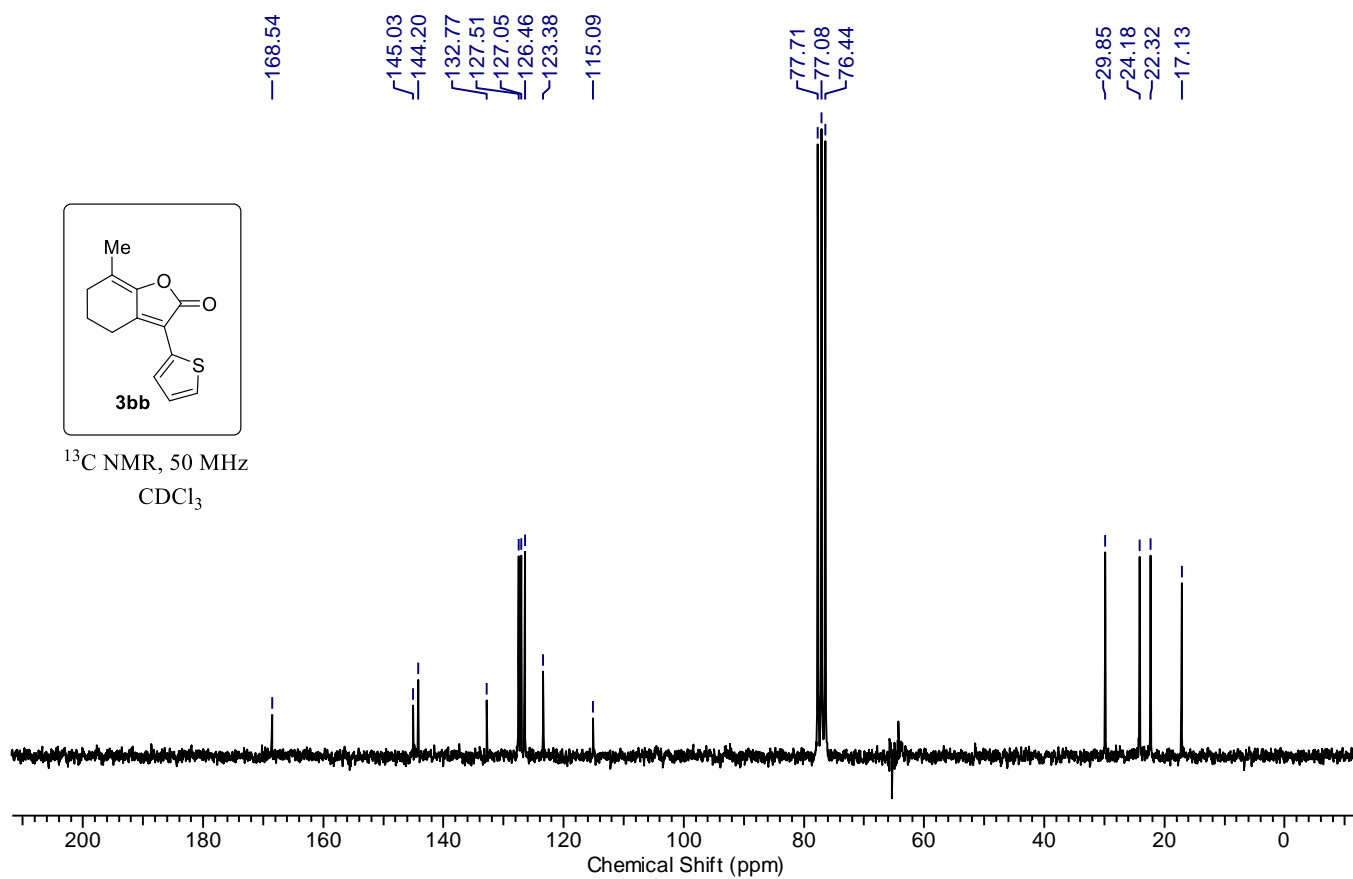
7-Methyl-3-(thiophen-2-yl)-5,6-dihydrobenzo-2(4H)-one (3bb):



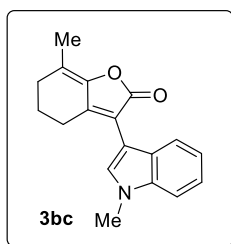
$^1\text{H NMR}$, 200 MHz
 CDCl_3



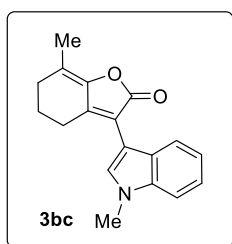
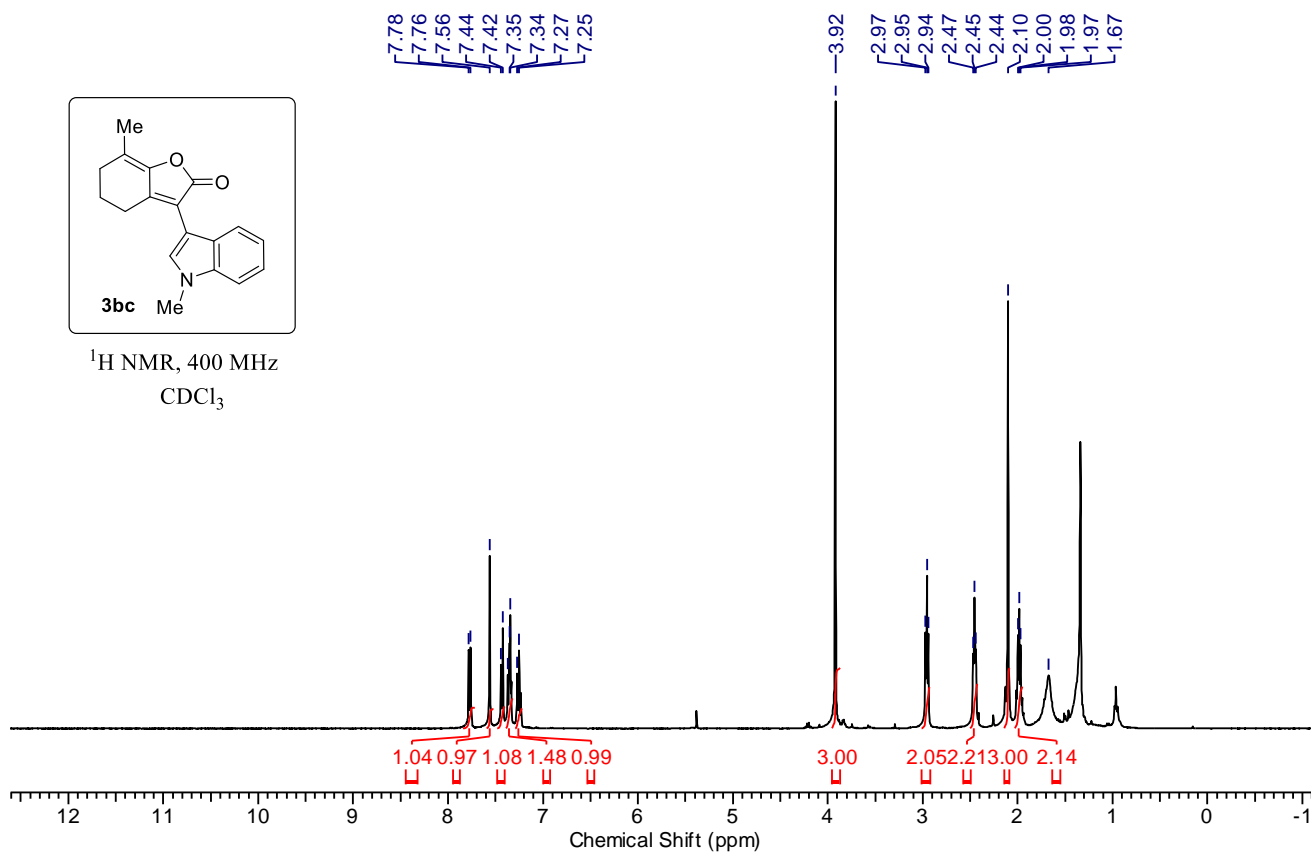
$^{13}\text{C NMR}$, 50 MHz
 CDCl_3



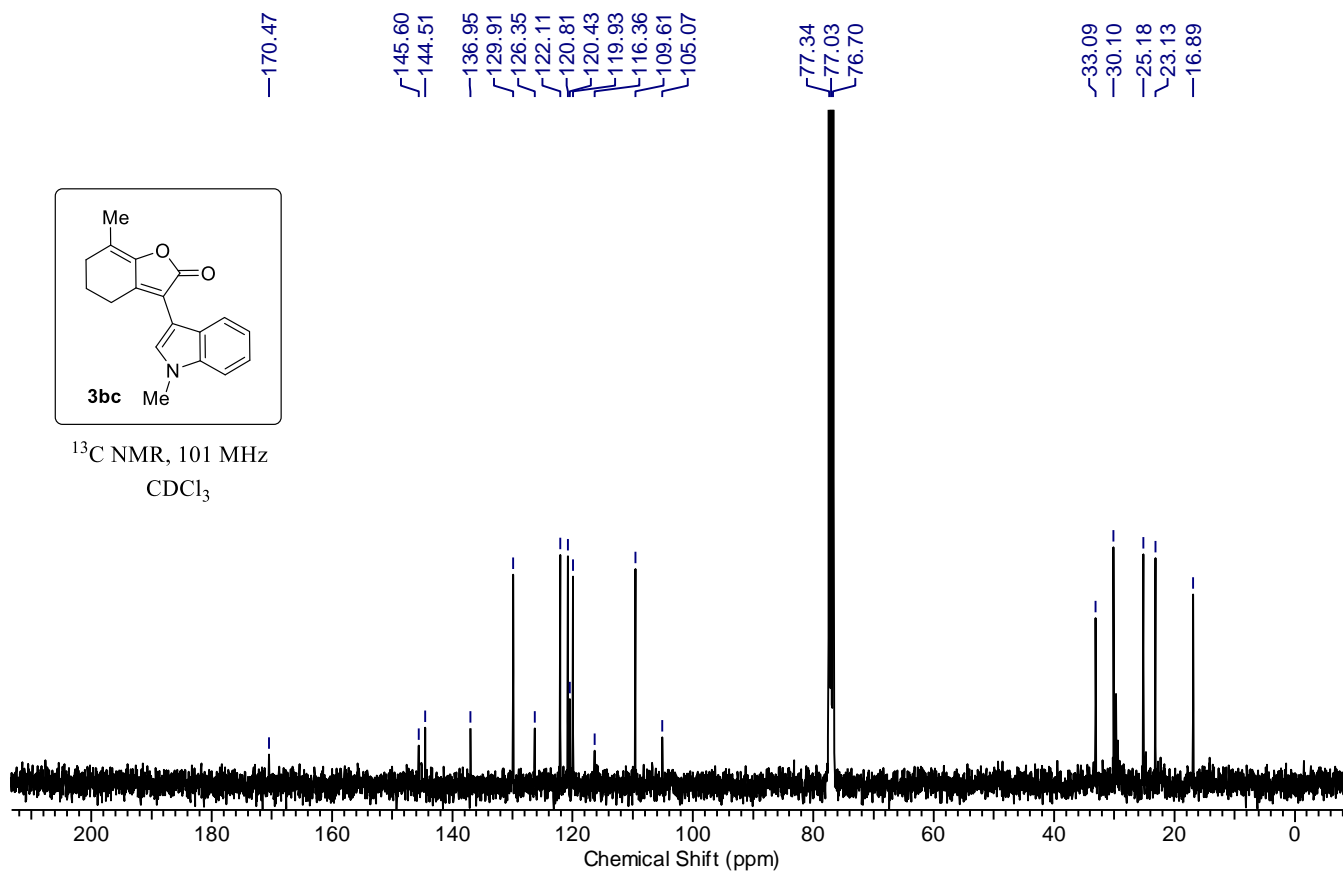
7-Methyl-3-(1-methyl-1*H*-indol-3-yl-5,6-dihydrobenzo-2(4*H*)-one (3bc):



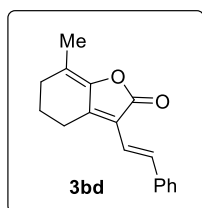
¹H NMR, 400 MHz
CDCl₃



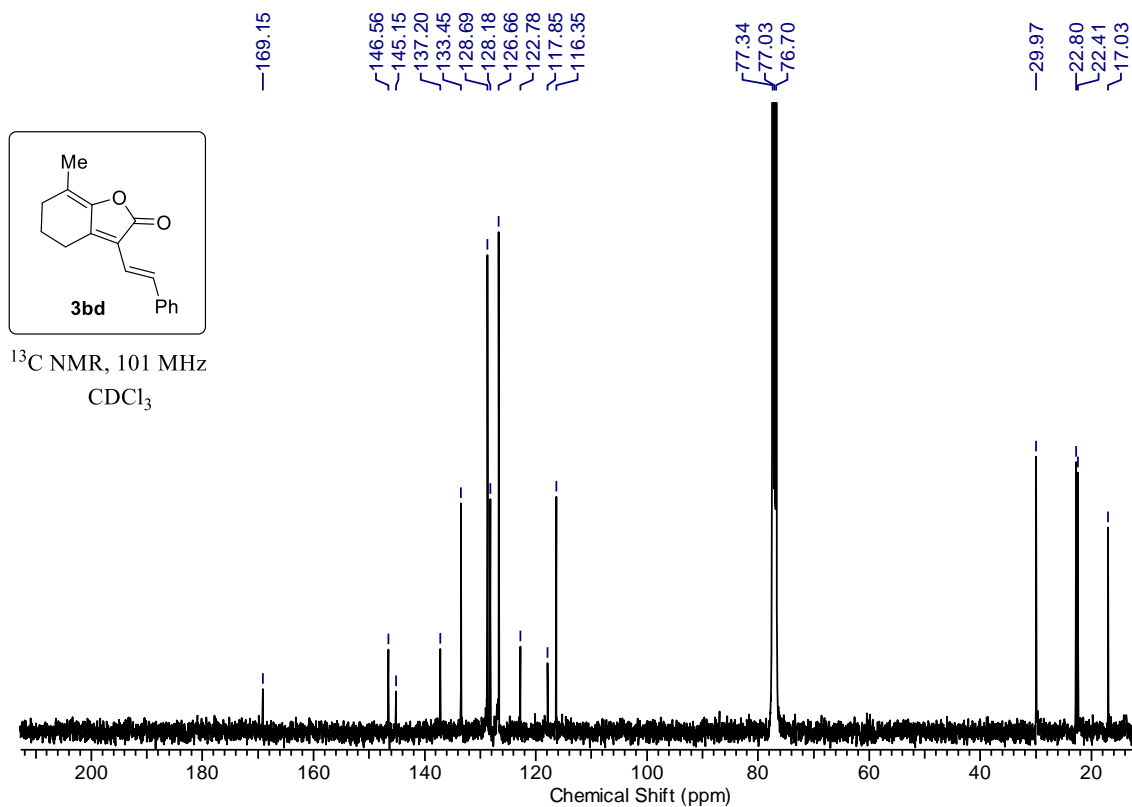
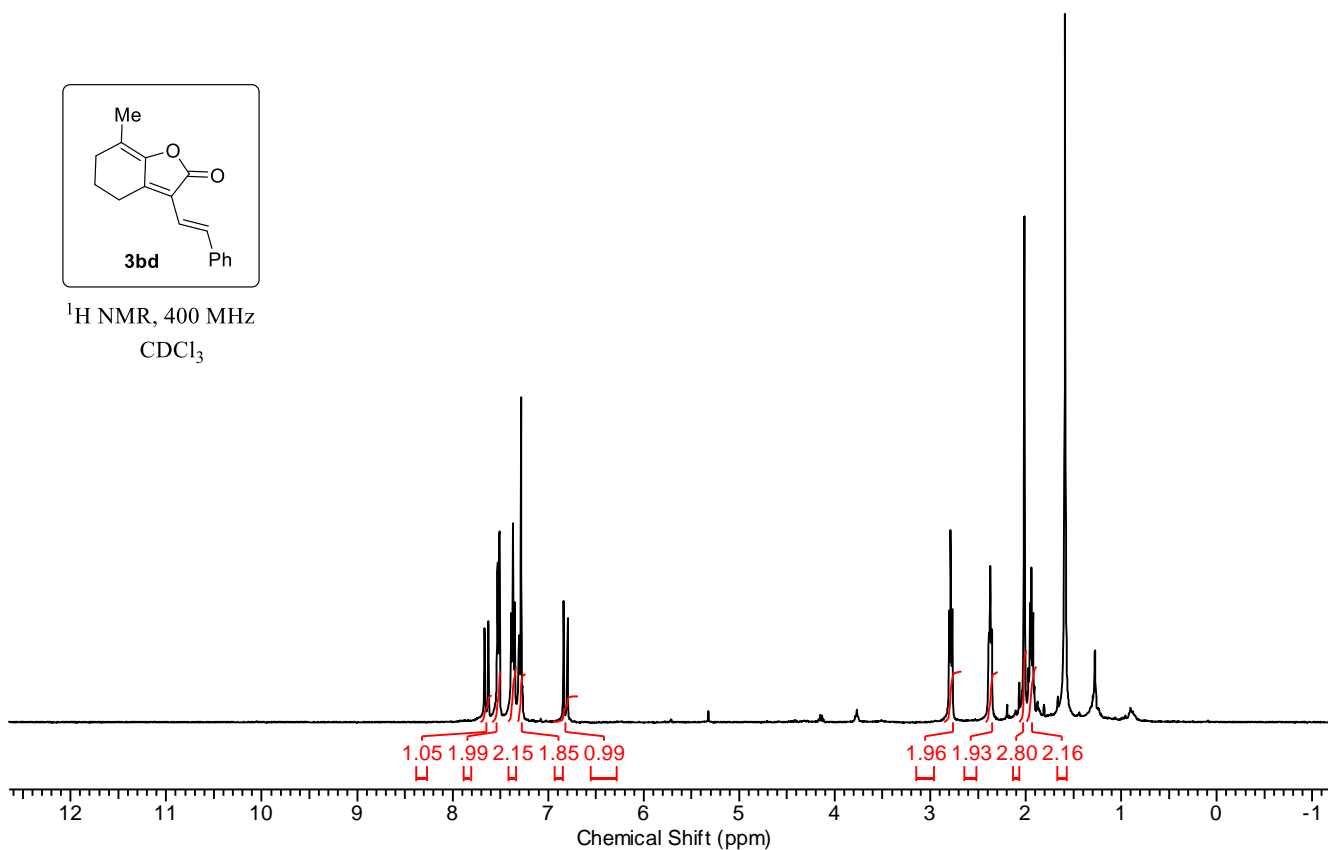
¹³C NMR, 101 MHz
CDCl₃



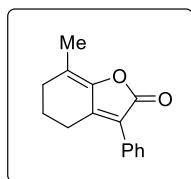
(E)- 7-Methyl-3-styryl-5,6-dihydrobenzo-2(4H)-one (3bd):



^1H NMR, 400 MHz
 CDCl_3



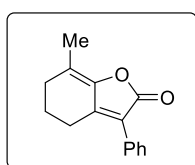
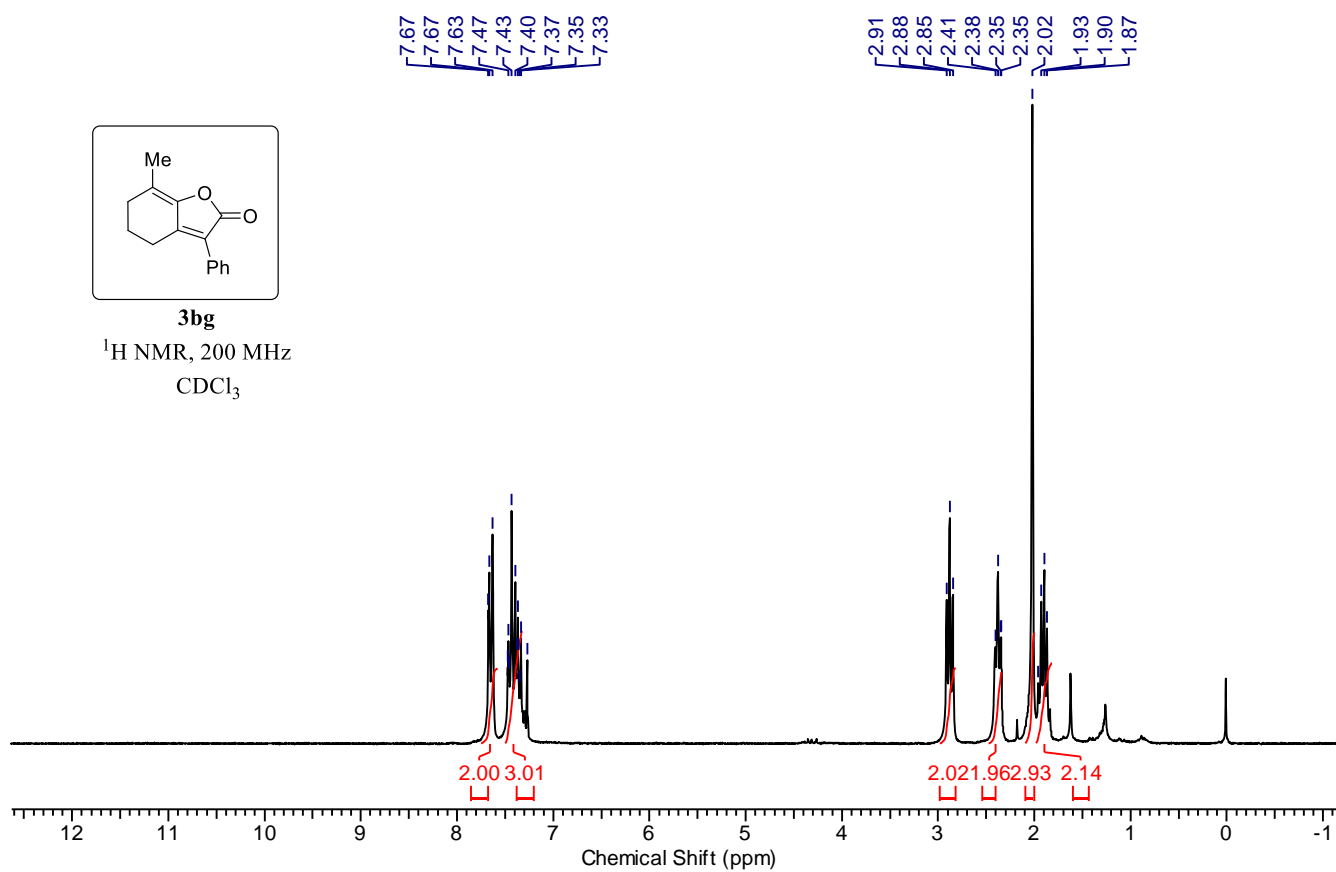
7-Methyl-3-phenyl-5,6-dihydrobenzo-2(4H)-one (3bg):



3bg

$^1\text{H NMR}$, 200 MHz

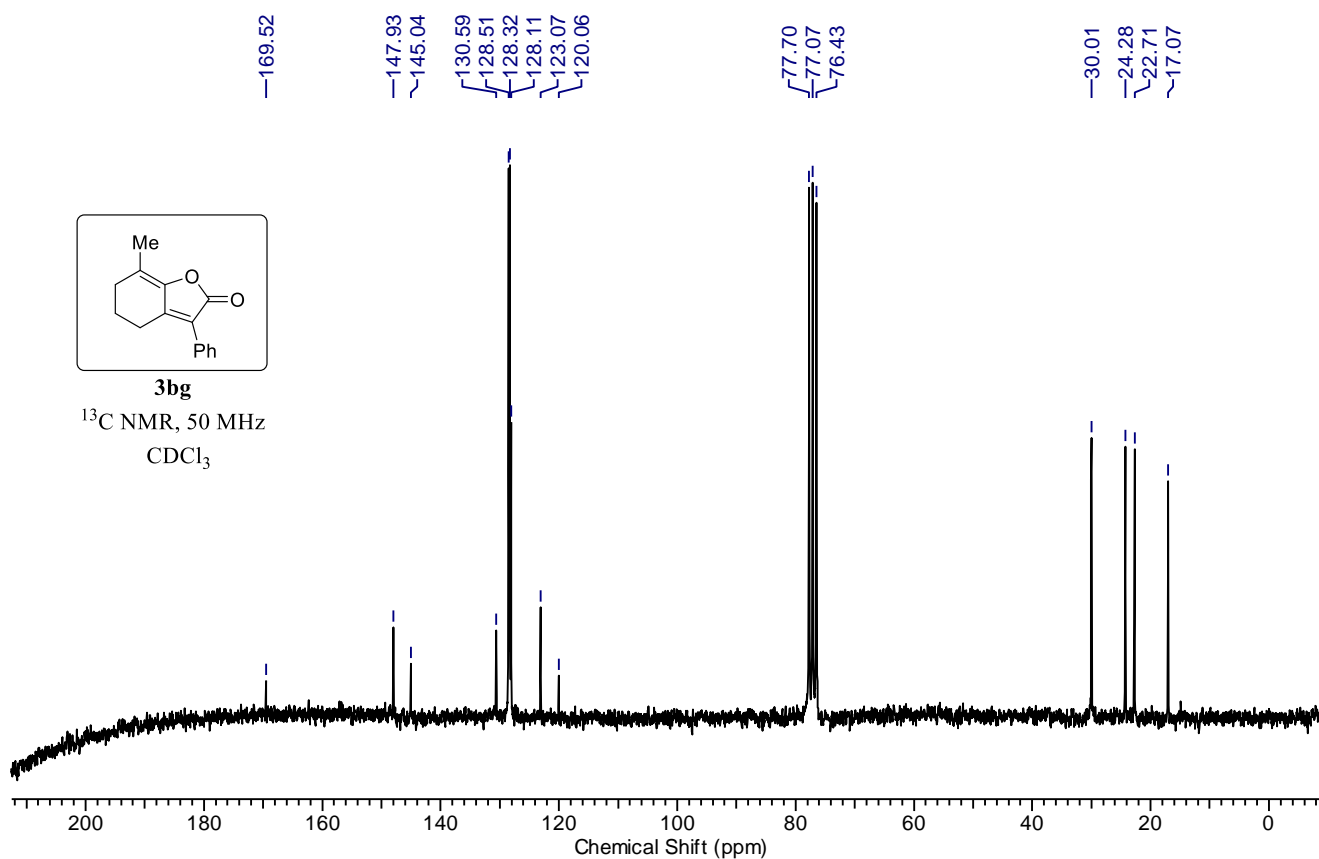
CDCl_3



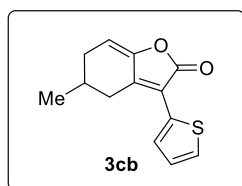
3bg

$^{13}\text{C NMR}$, 50 MHz

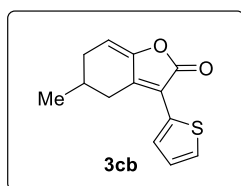
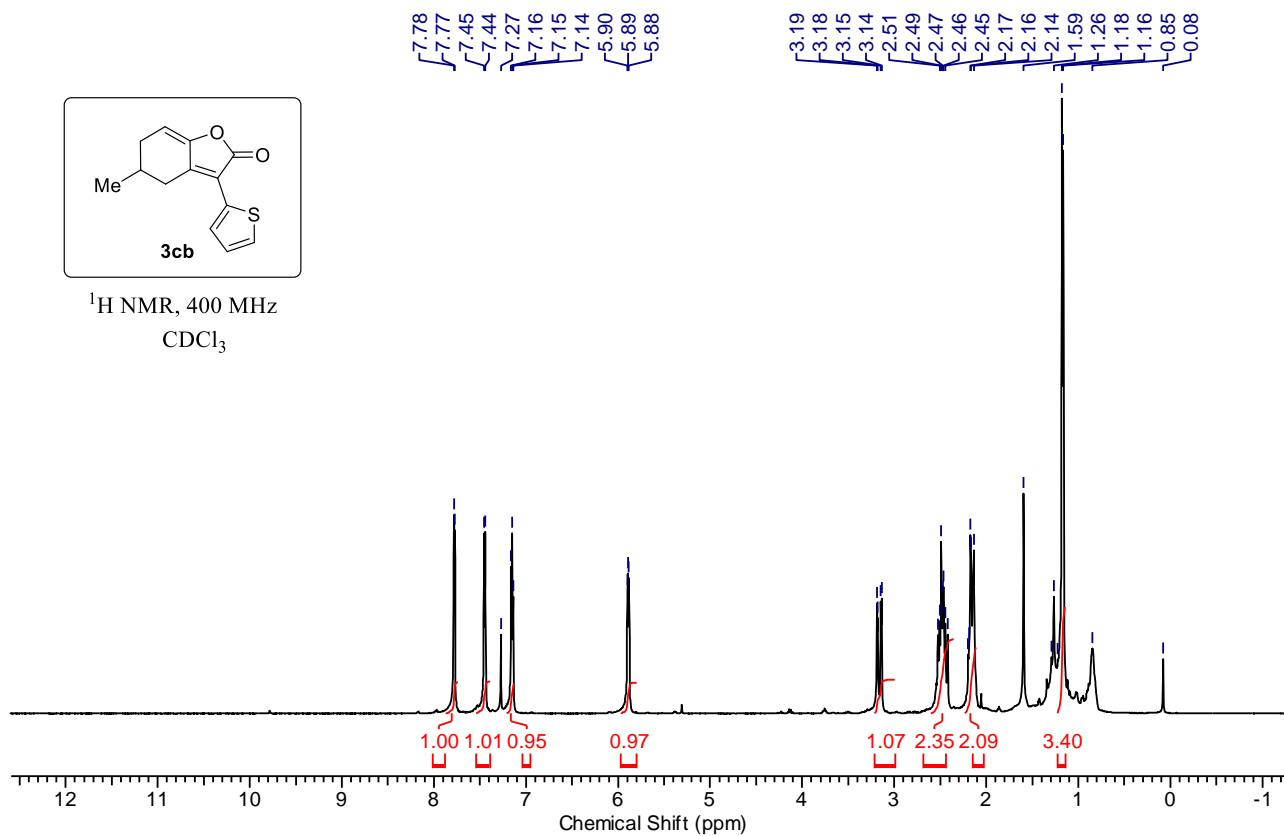
CDCl_3



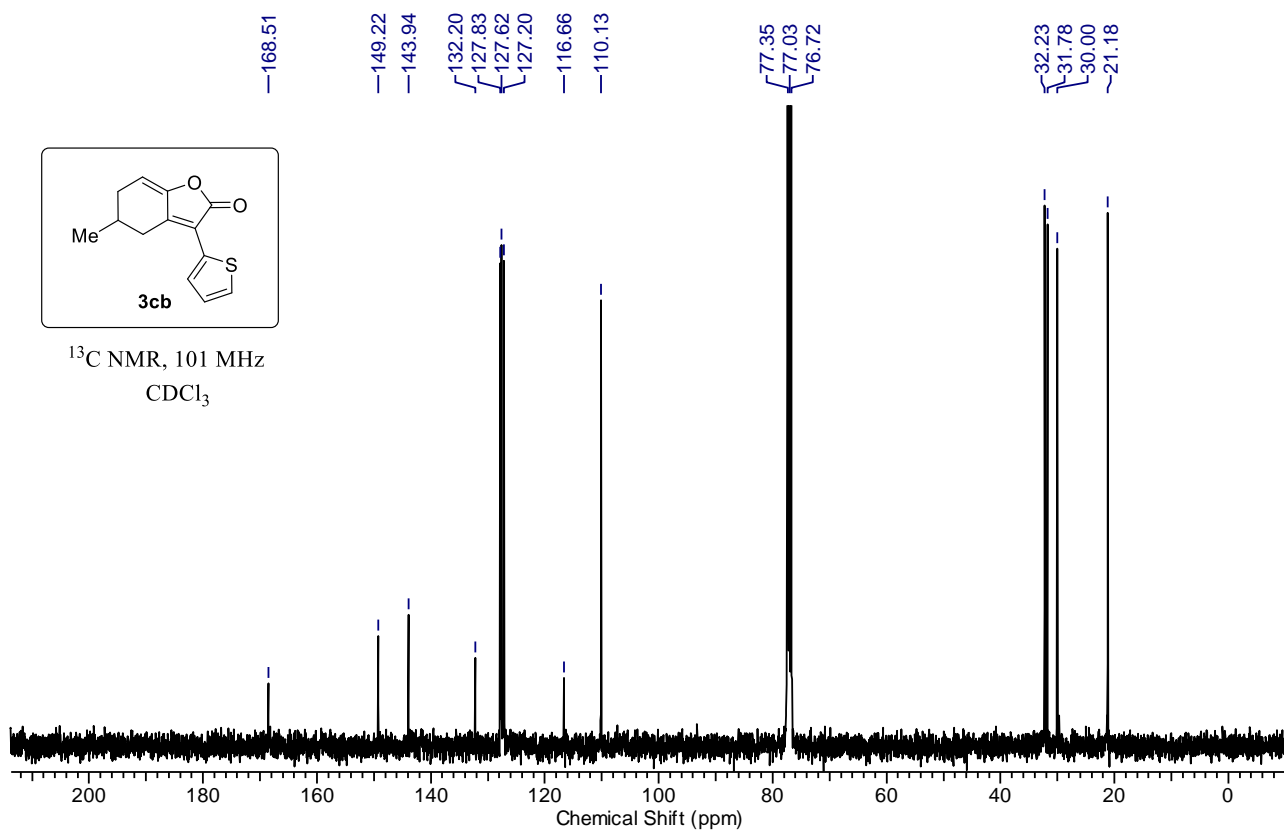
5-Methyl-3-(thiophen-2-yl)-5,6-dihydrobenzo-2(4H)-one (3cb):



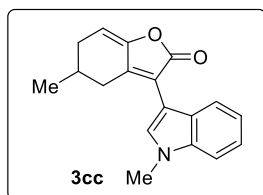
^1H NMR, 400 MHz
 CDCl_3



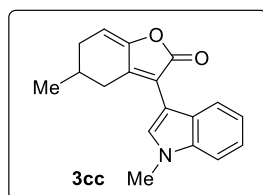
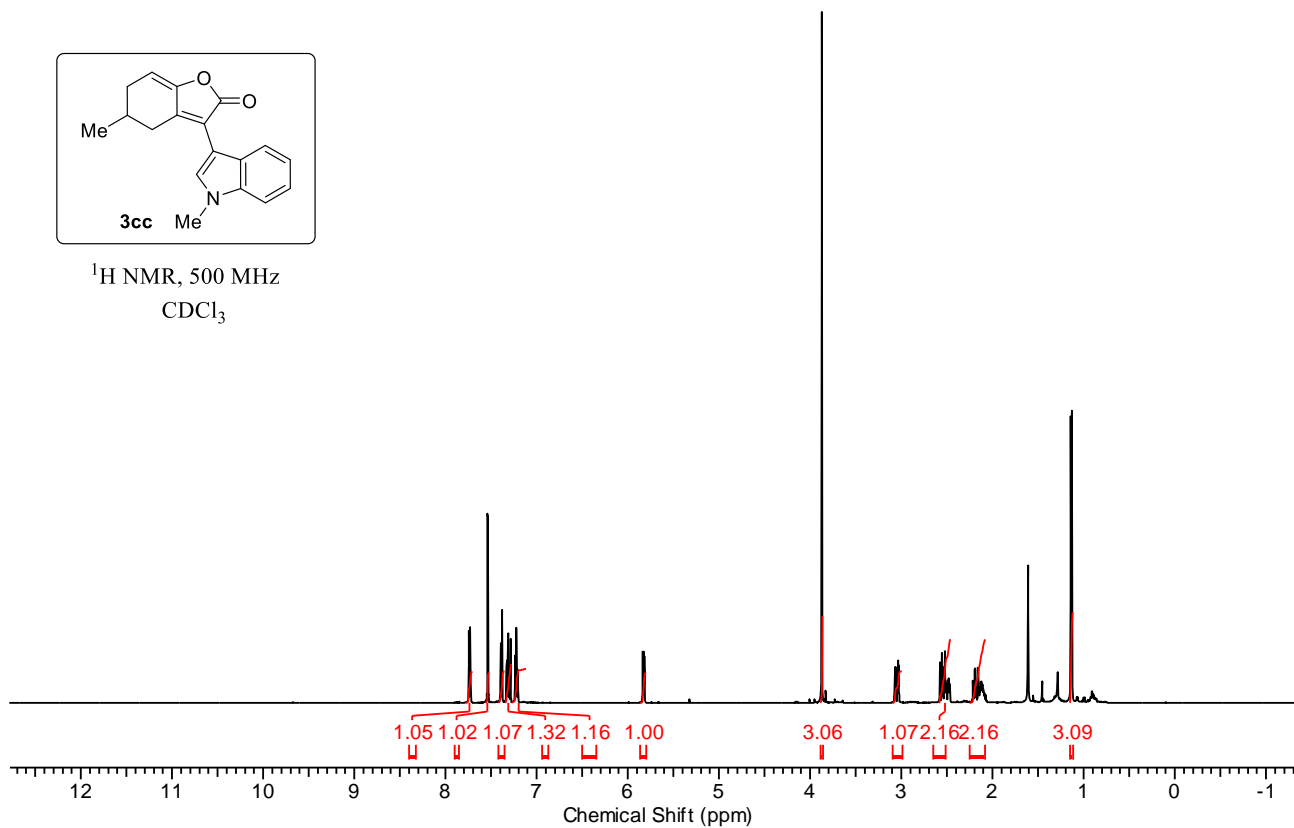
^{13}C NMR, 101 MHz
 CDCl_3



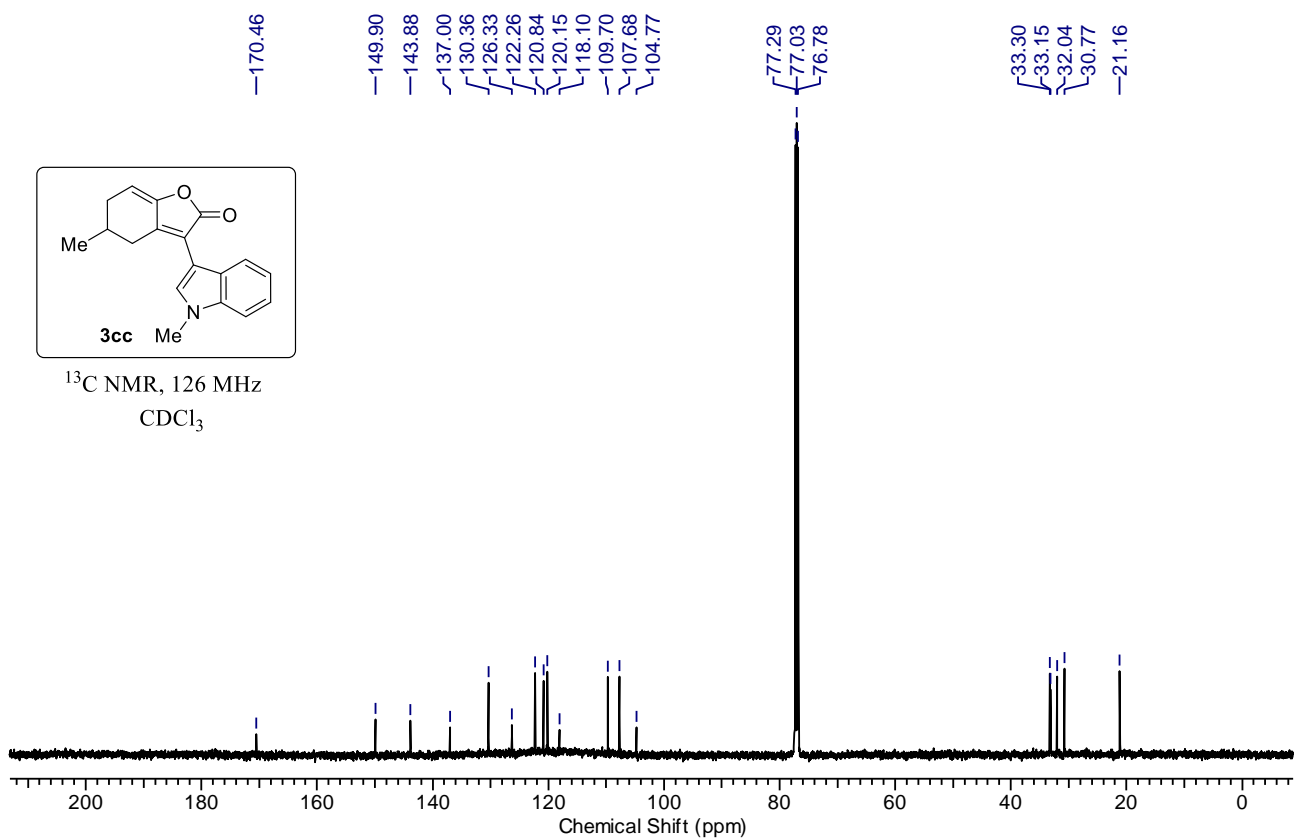
5-Methyl-3-(1-methyl-1*H*-indol-3-yl)-5,6-dihydrobenzo-2(4*H*)-one (3cc):



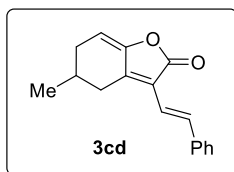
¹H NMR, 500 MHz
CDCl₃



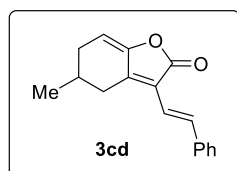
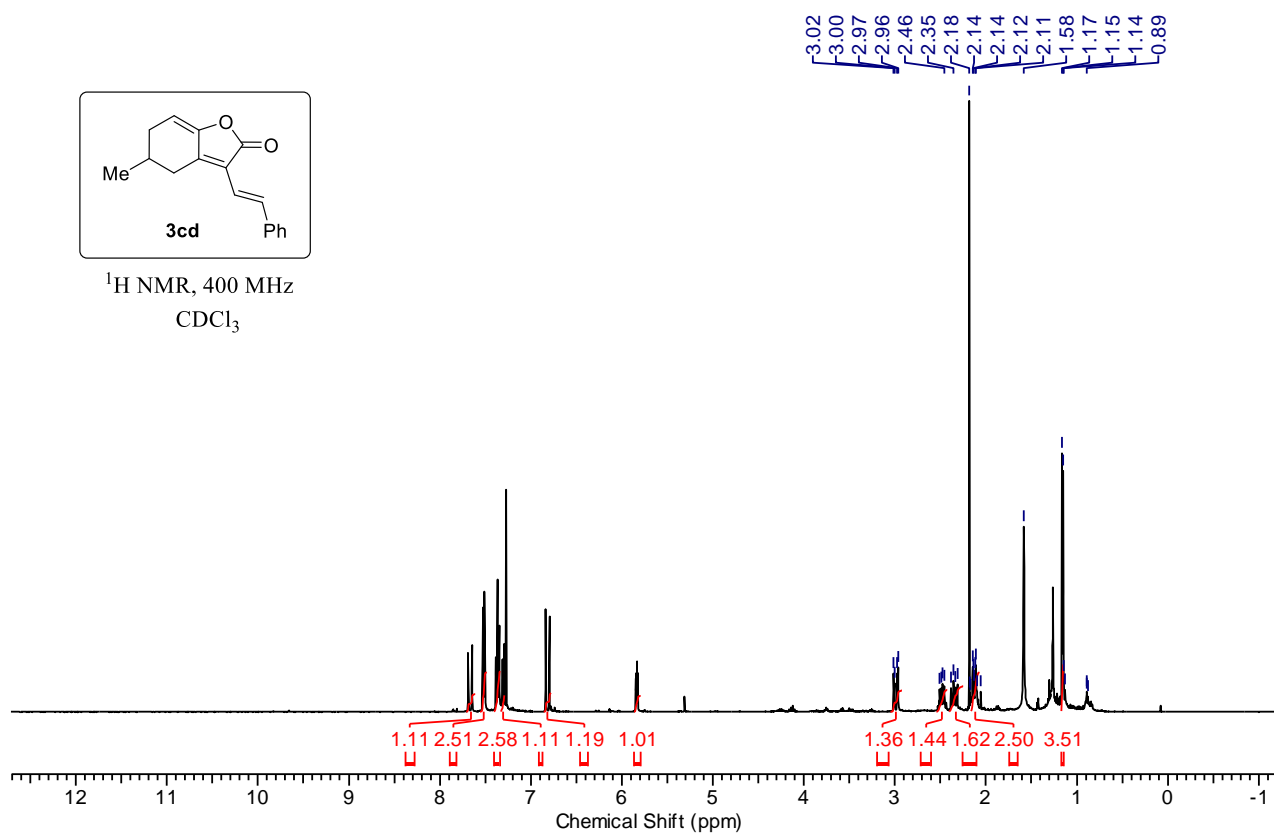
¹³C NMR, 126 MHz
CDCl₃



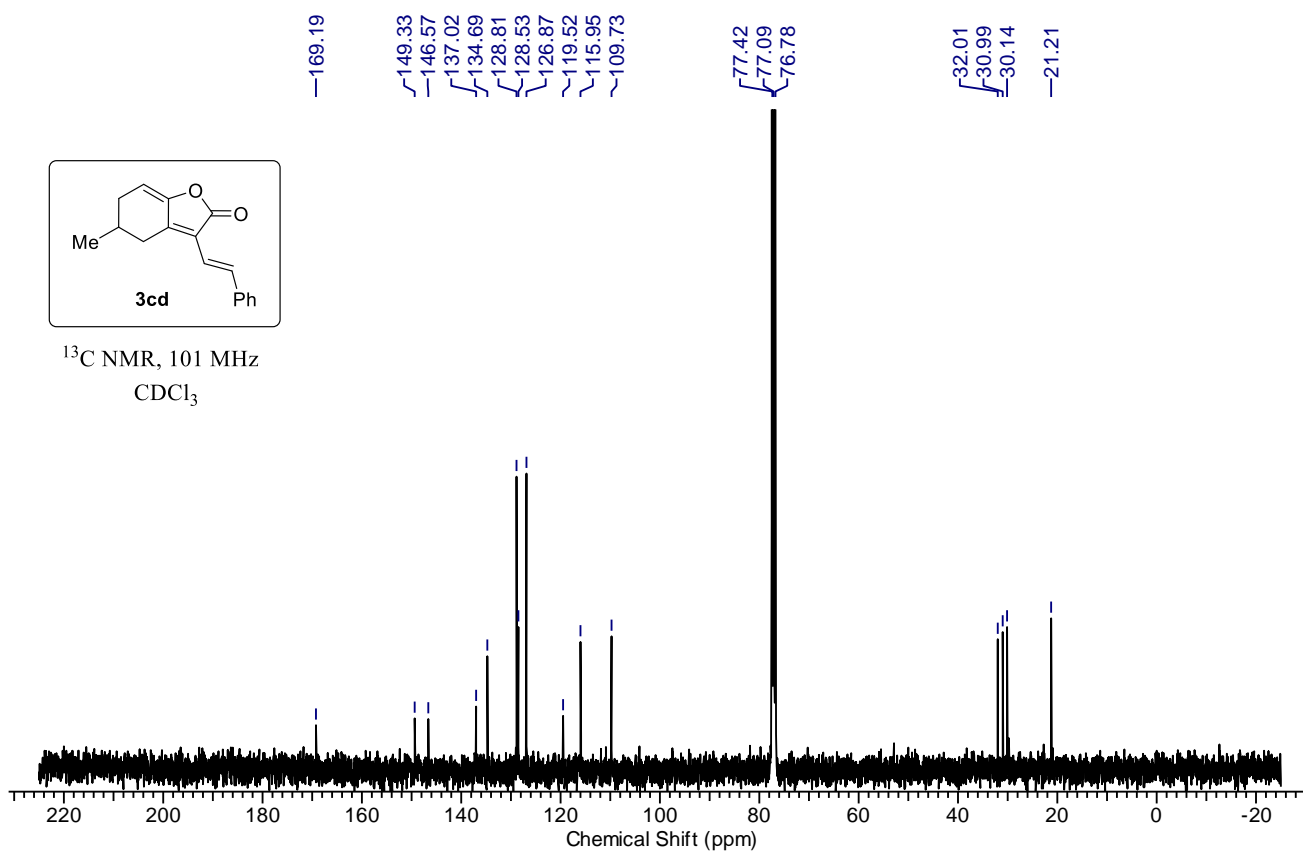
(E)- 5-Methyl-3-styryl-5,6-dihydrobenzo-2(4H)-one (3cd):



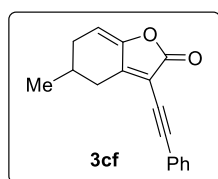
¹H NMR, 400 MHz
CDCl₃



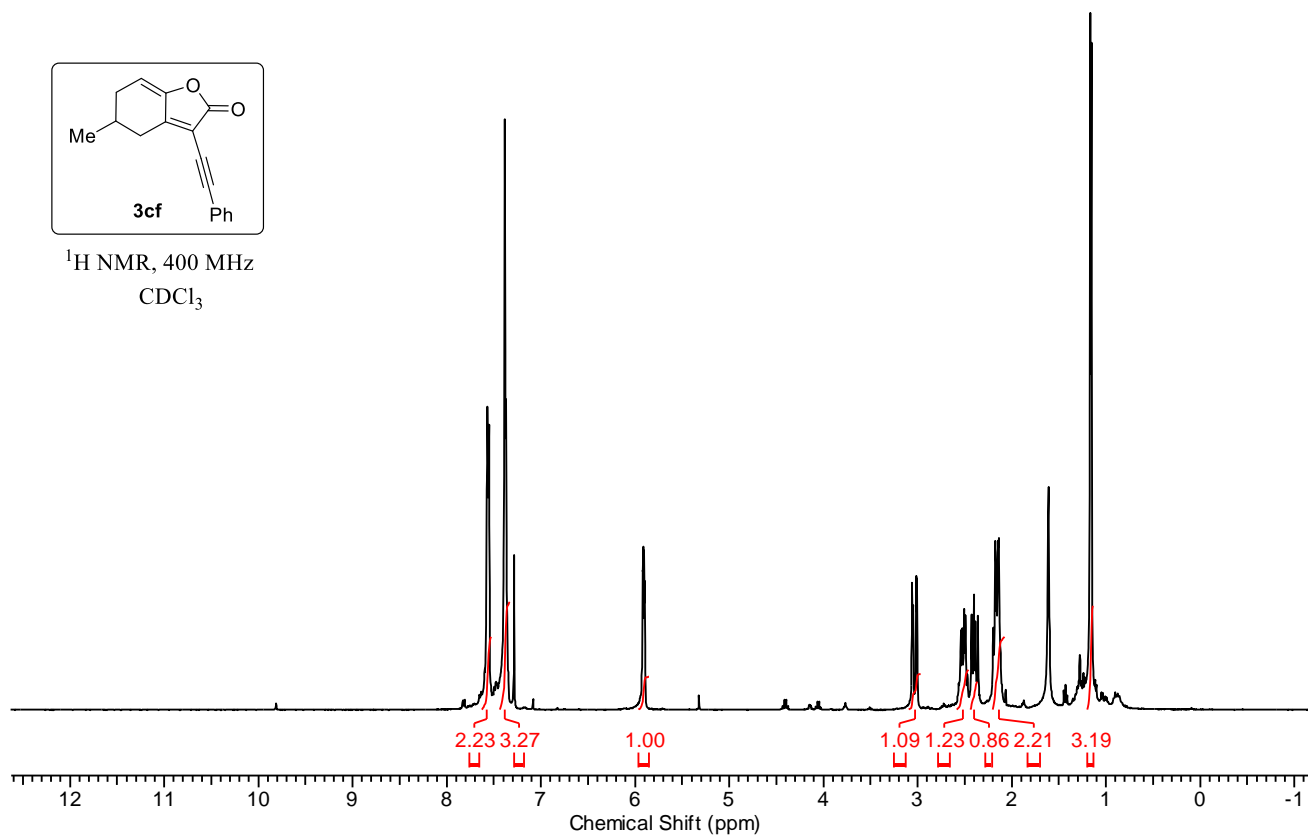
¹³C NMR, 101 MHz
CDCl₃



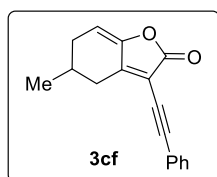
5-Methyl-3-(phenylethynyl)-5,6-dihydrobenzofuran-2(4H)-one (3cf):



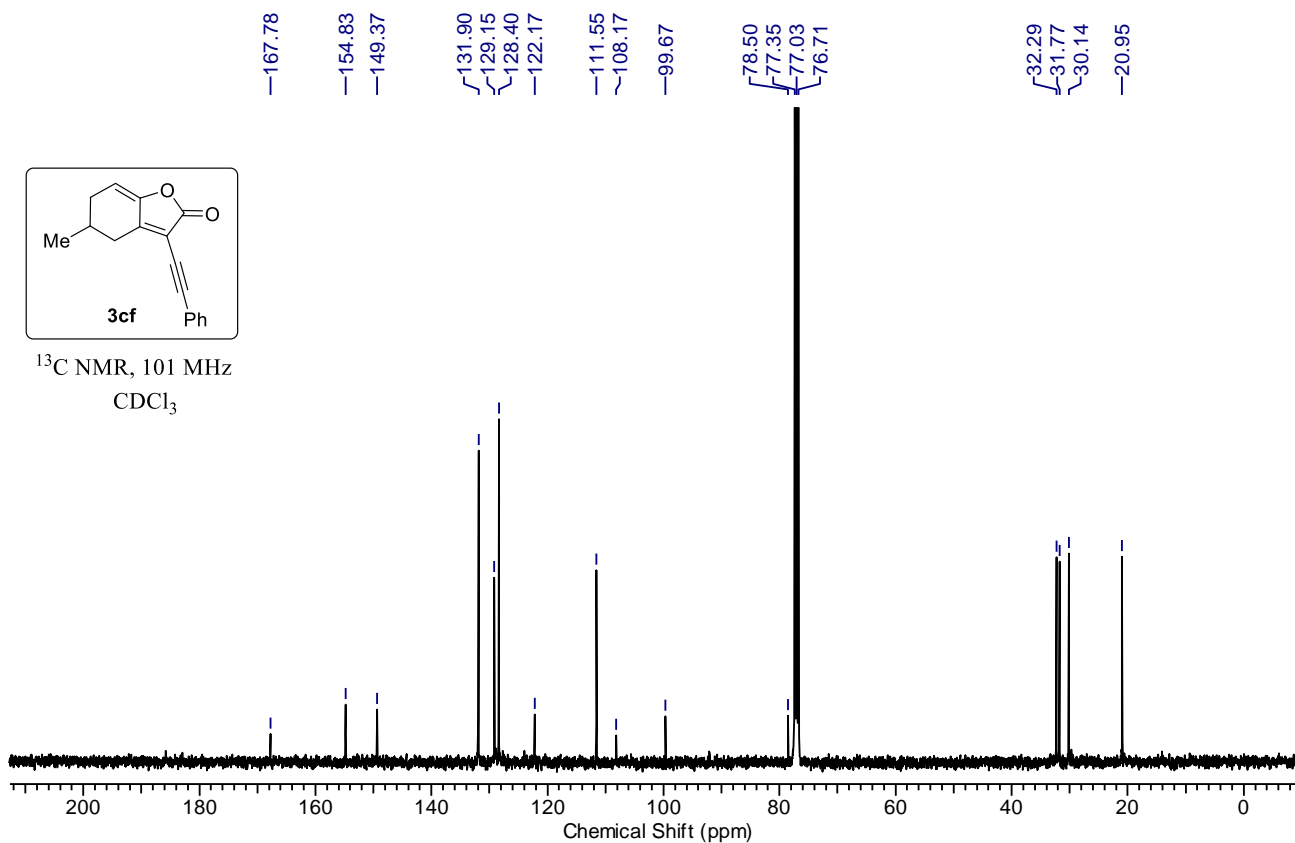
^1H NMR, 400 MHz
 CDCl_3



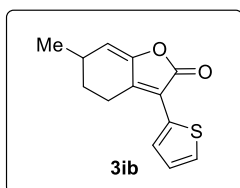
—167.78
—154.83
—149.37
—131.90
—129.15
—128.40
—122.17
—111.55
—108.17
—99.67
—78.50
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—77.03
—76.71
—32.29
—31.77
—30.14
—20.95



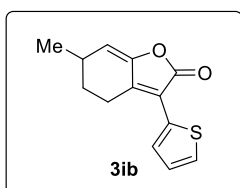
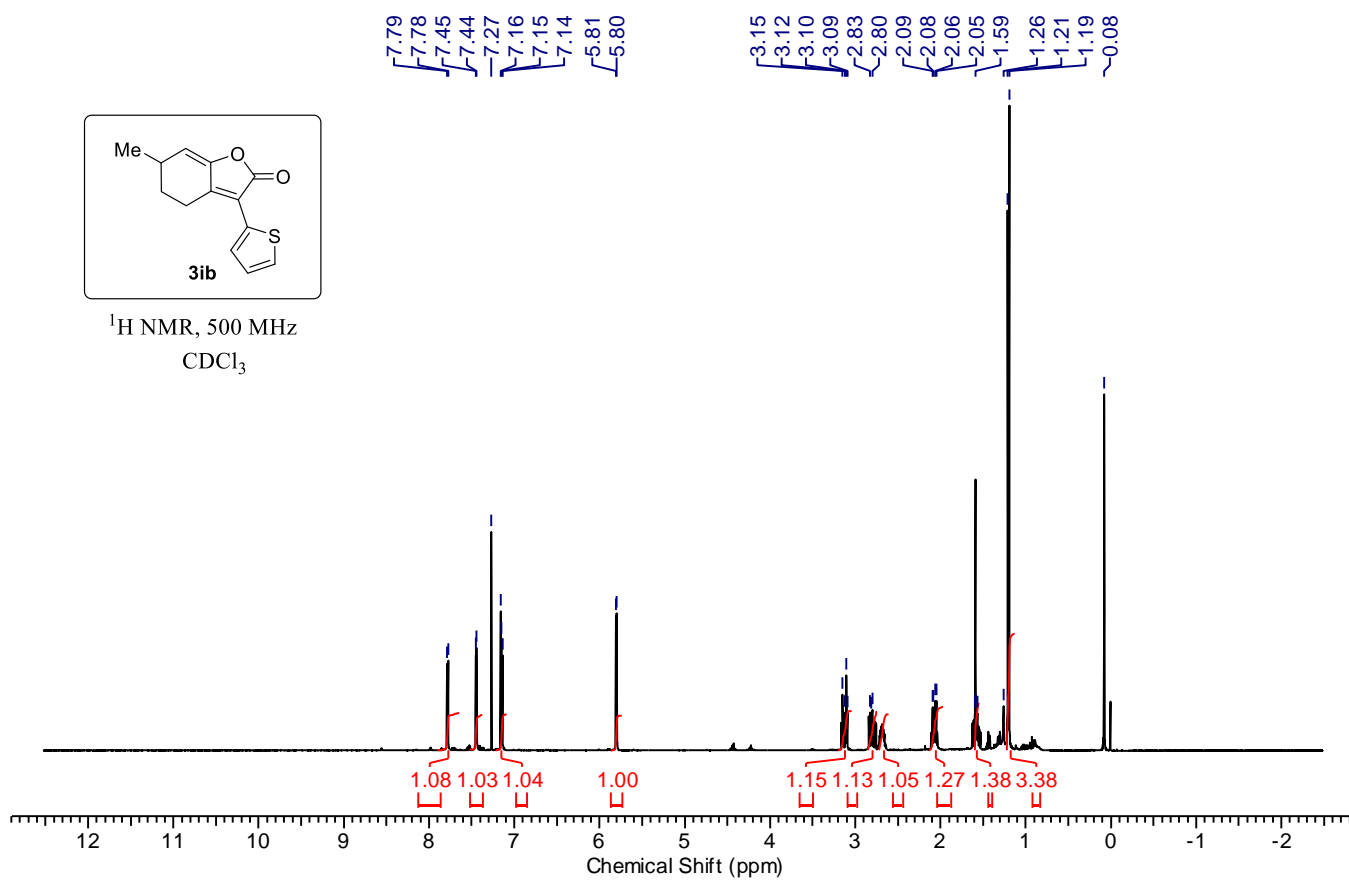
^{13}C NMR, 101 MHz
 CDCl_3



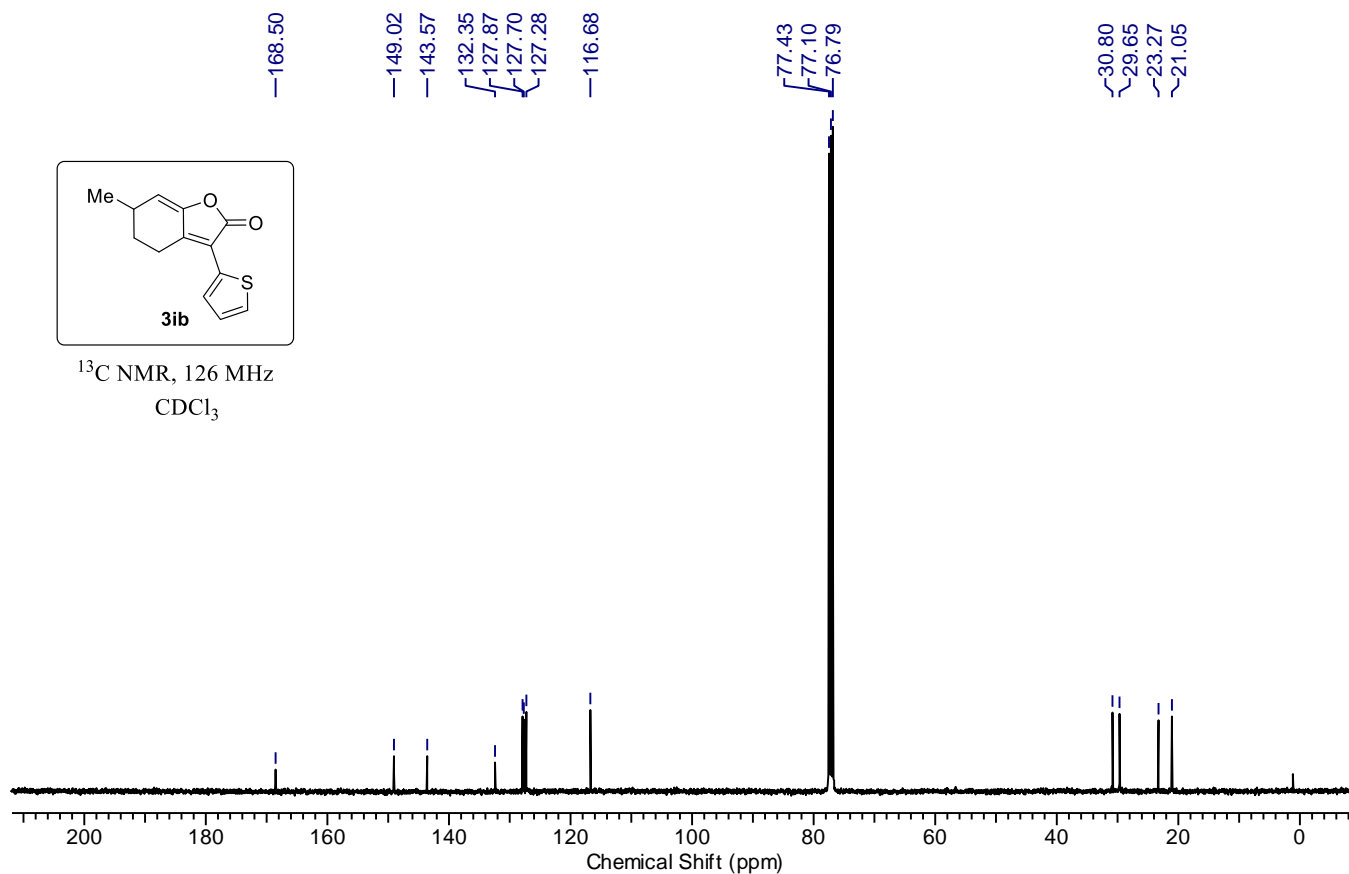
6-Methyl-3-(thiophen-2-yl)-5,6-dihydrobenzofuran-2(4H)-one (3ib):



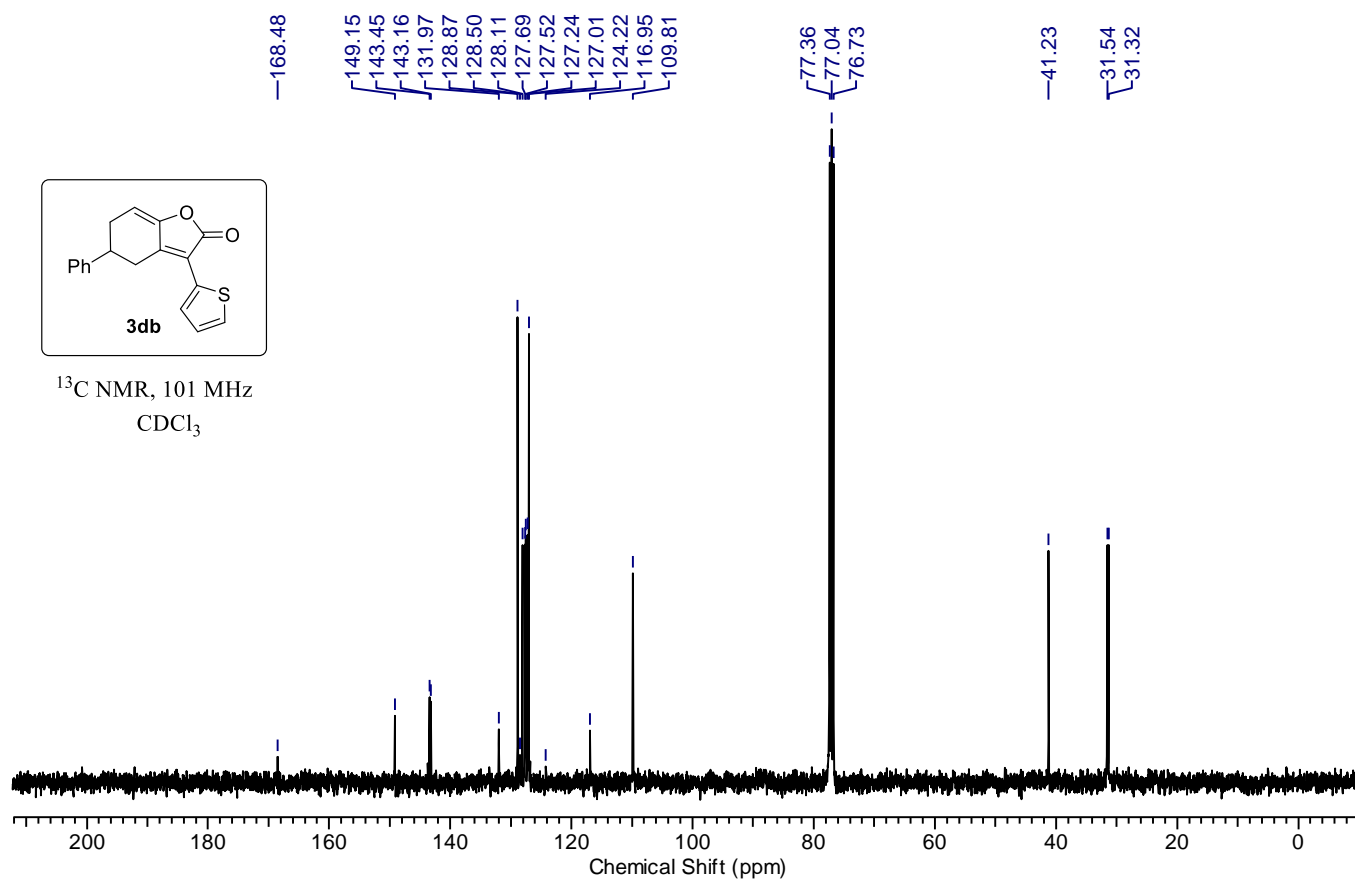
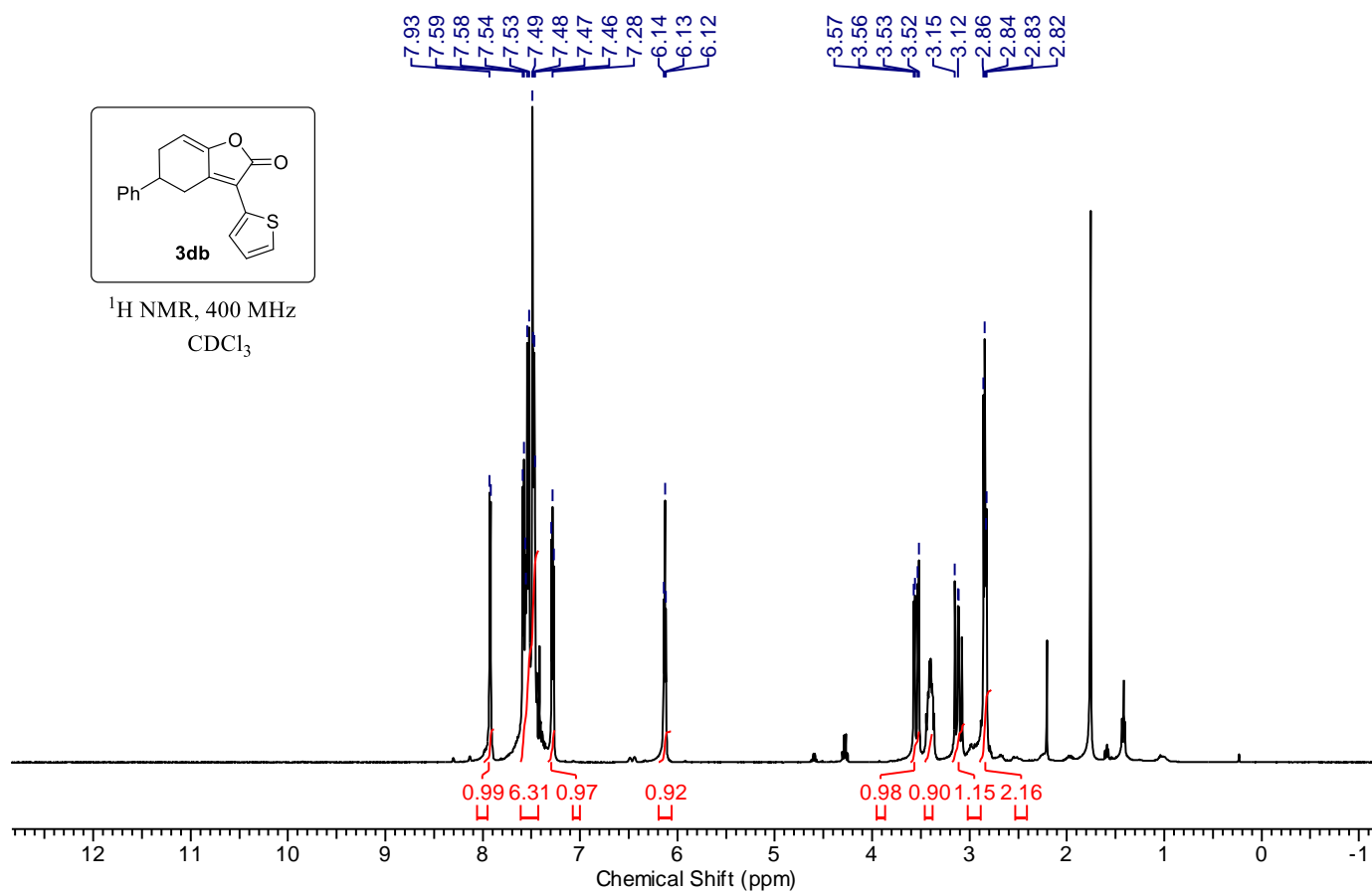
¹H NMR, 500 MHz
CDCl₃



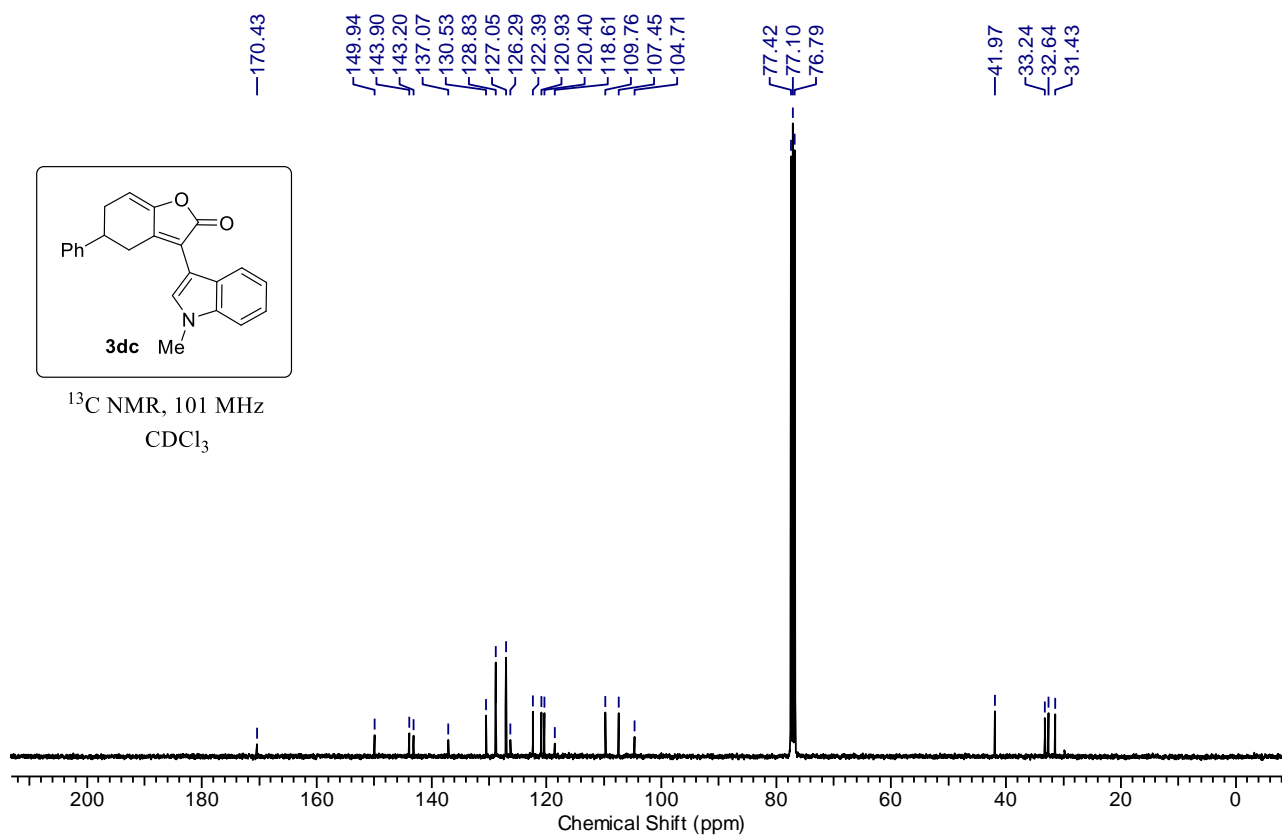
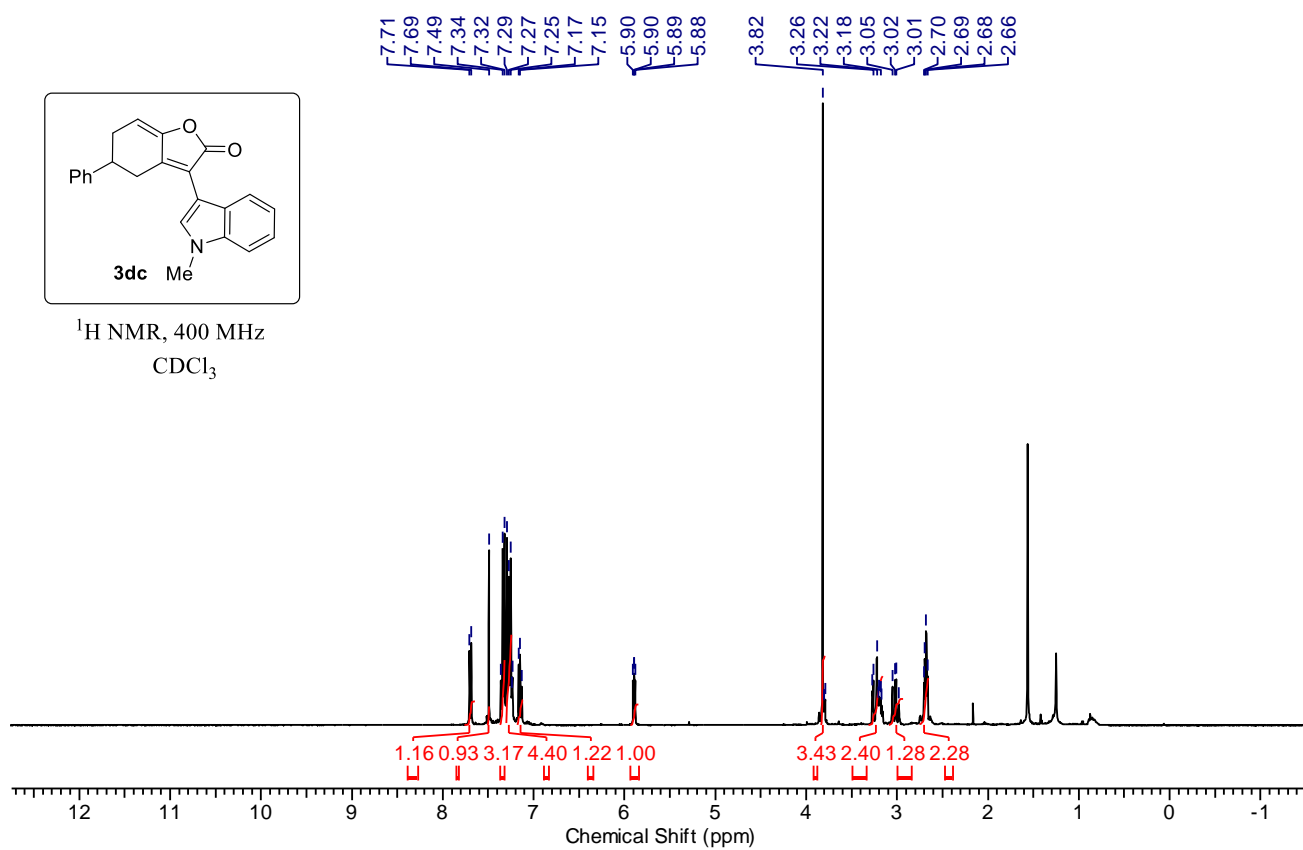
¹³C NMR, 126 MHz
CDCl₃



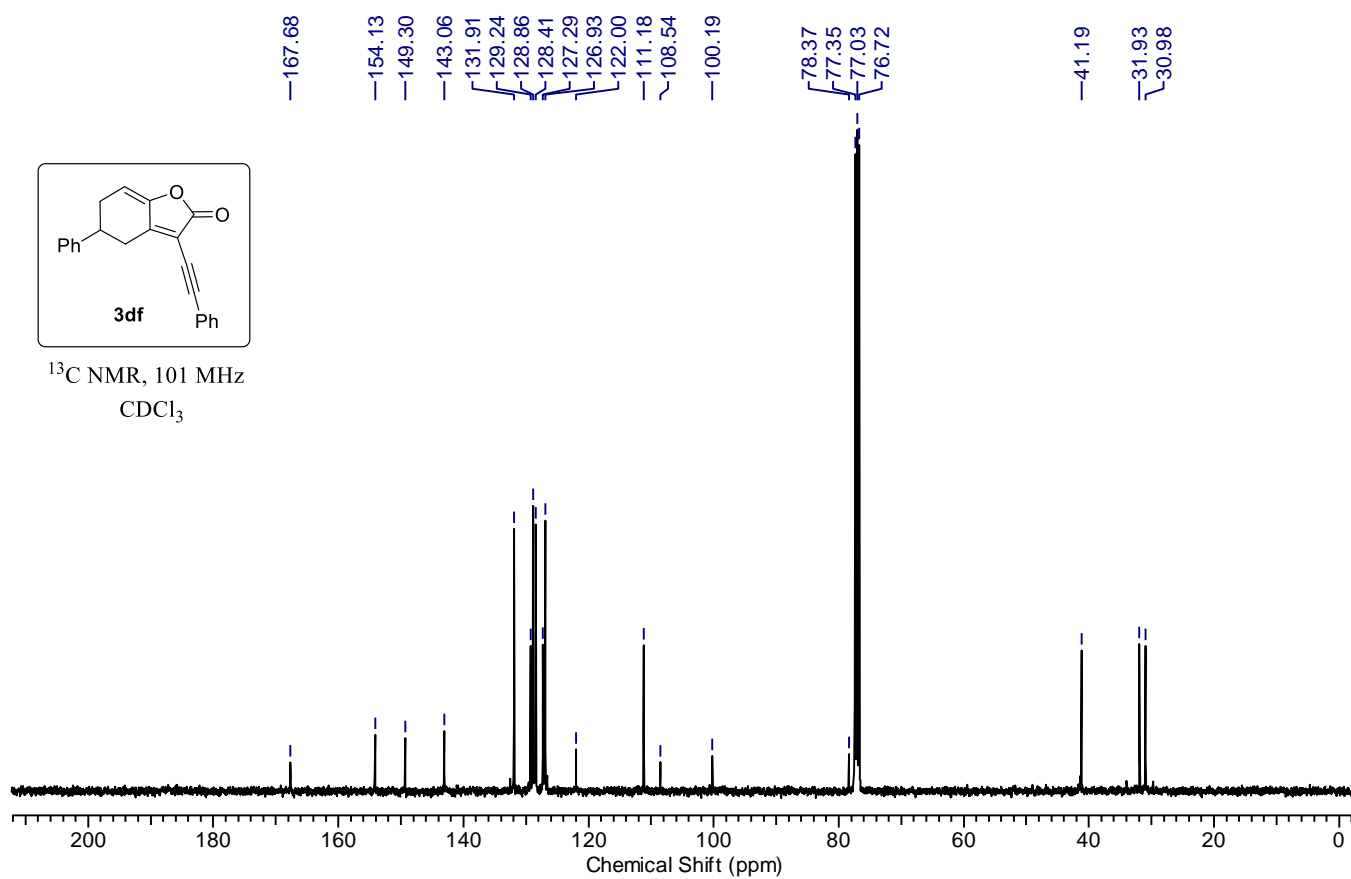
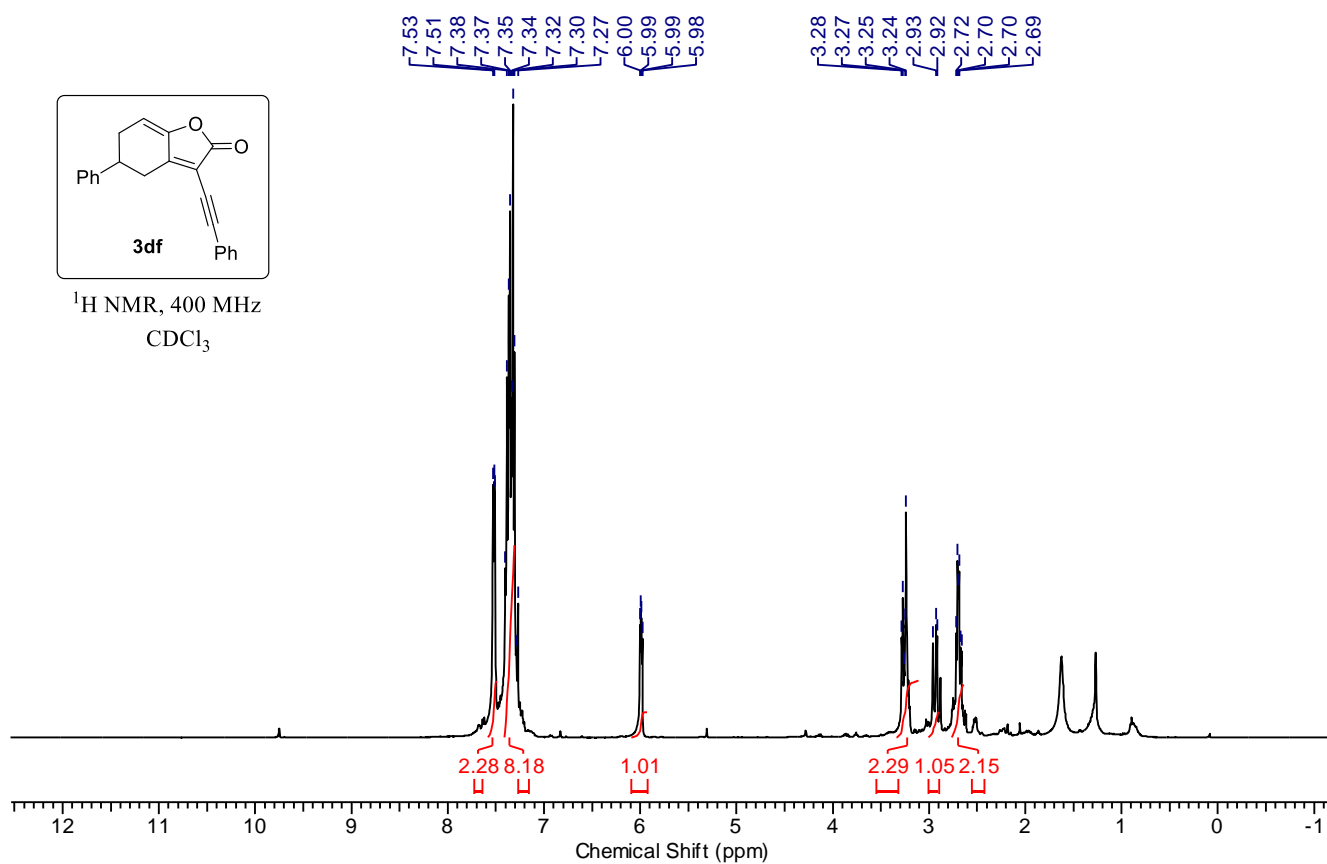
5-Phenyl-3-(thiophen-2-yl)-5,6-dihydrobenzo-2(4H)-one (3db):



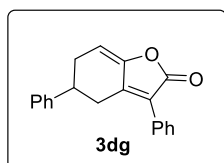
3-(1-Methyl-1*H*-indol-3-yl)-5,6-dihydrobenzo-2(4*H*)-one (3dc):



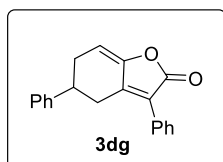
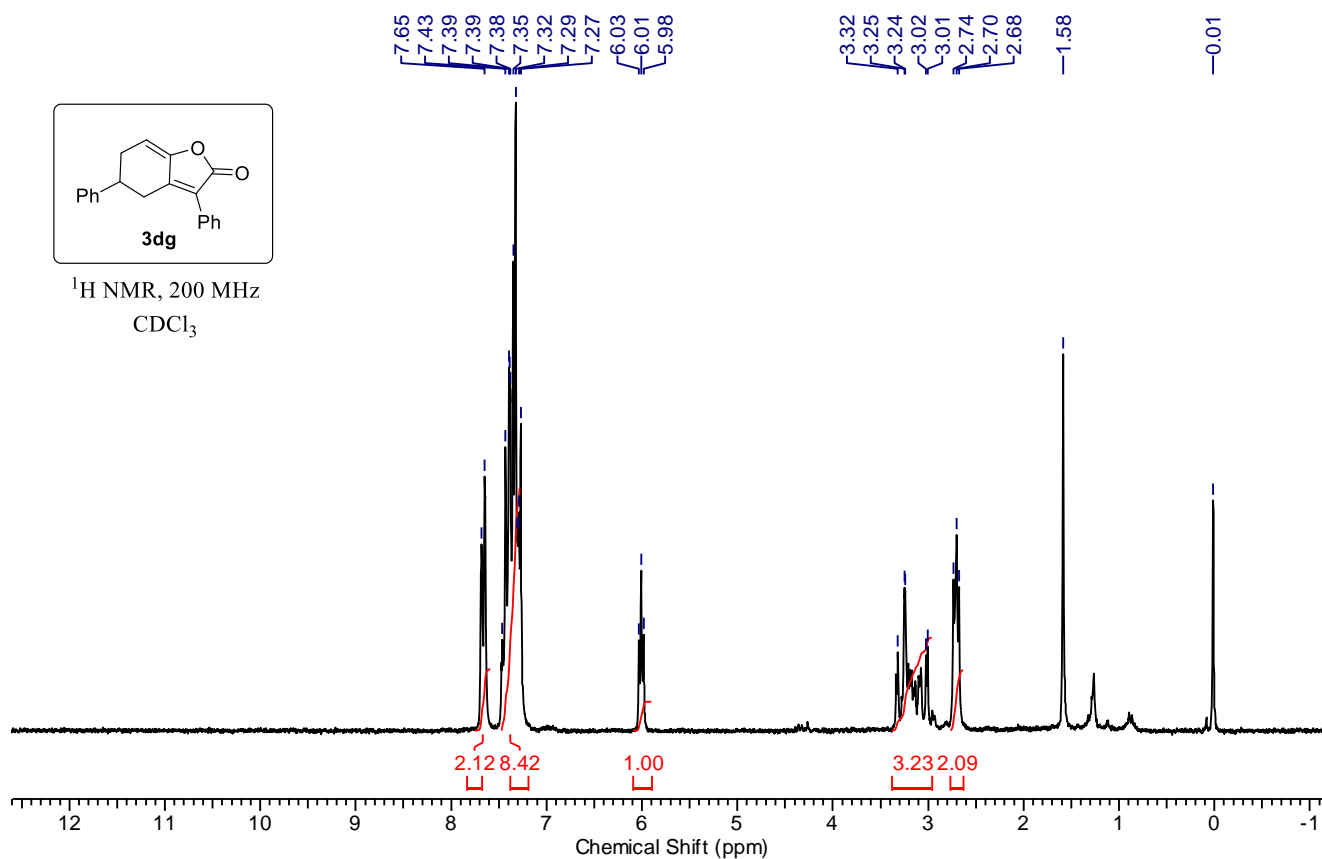
5-Phenyl-3-(phenylethynyl)-5,6-dihydrobenzo-2(4H)-one (3df):



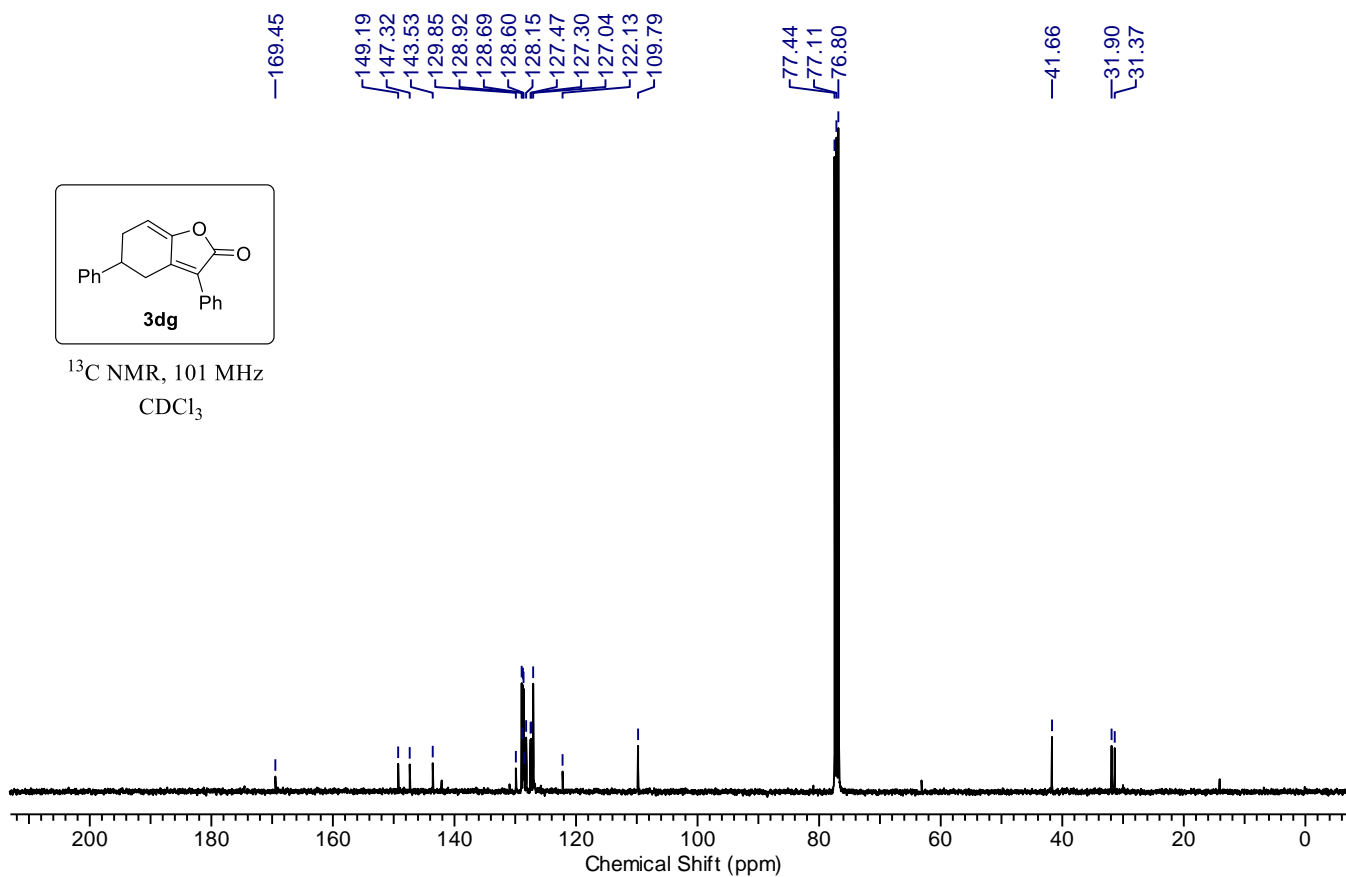
3,5-Diphenyl-5,6-dihydrobenzofuran-2(4H)-one (3dg):



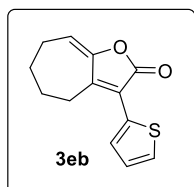
$^1\text{H NMR}$, 200 MHz
 CDCl_3



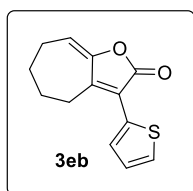
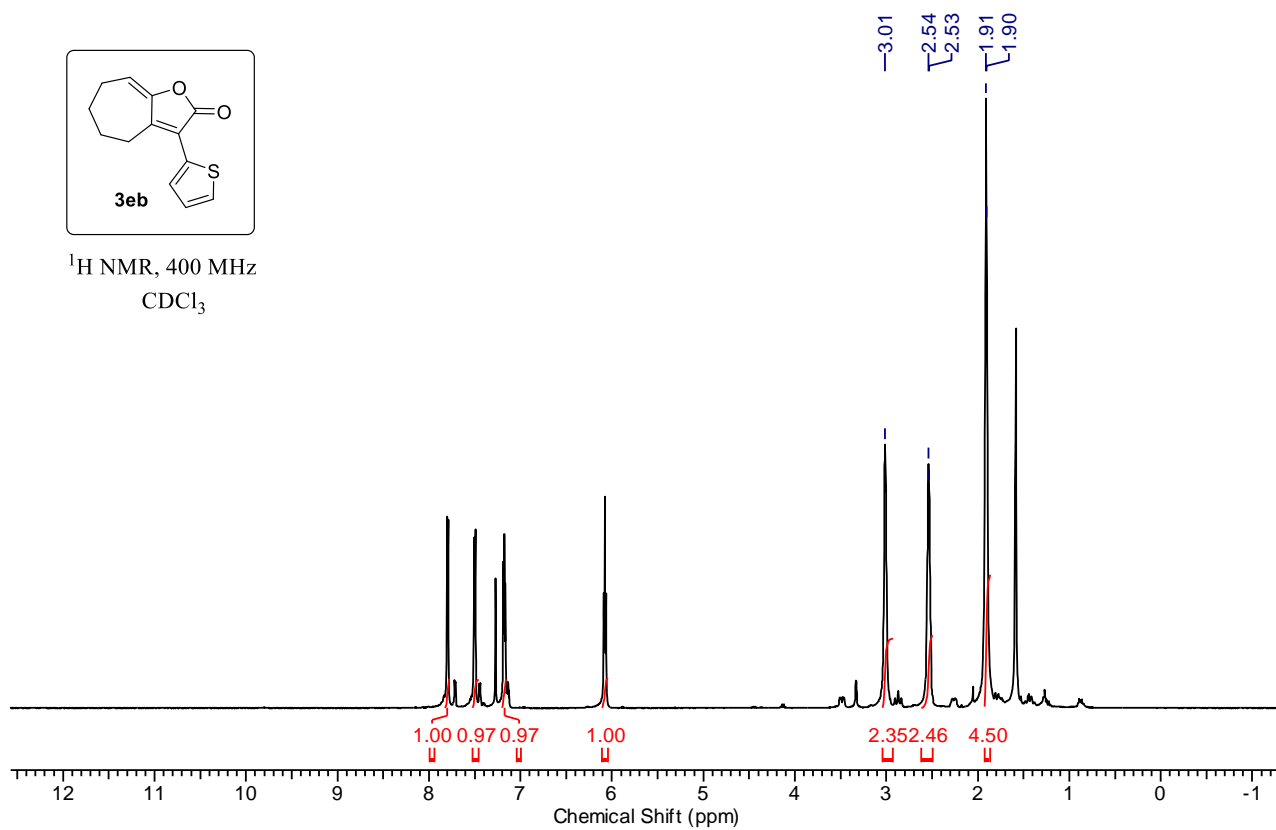
$^{13}\text{C NMR}$, 101 MHz
 CDCl_3



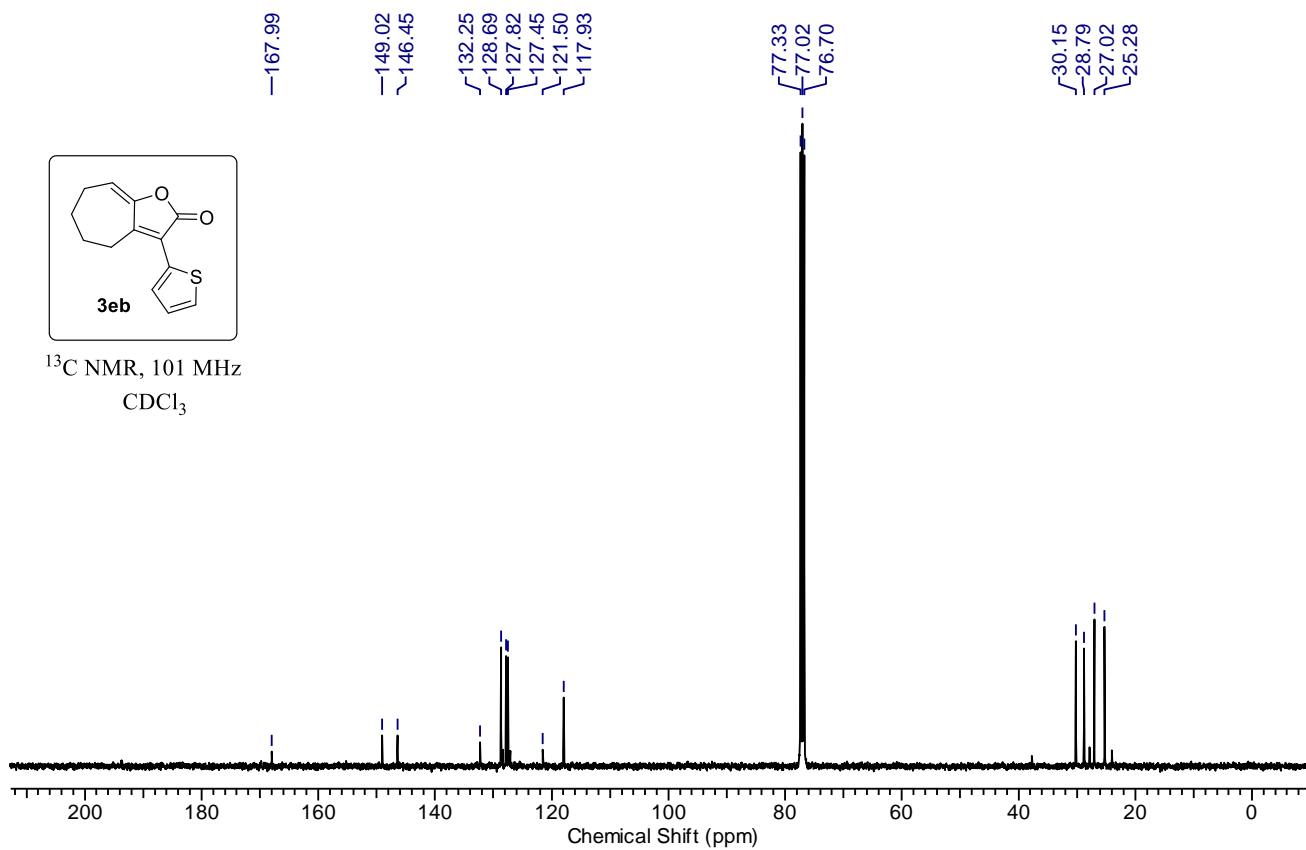
3-(Thiophen-2-yl)-4,5,6,7-tetrahydro-2H-cyclohepta[b]-2-one (3eb):



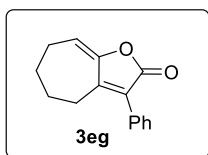
^1H NMR, 400 MHz
 CDCl_3



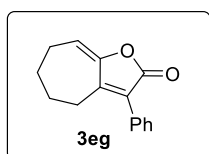
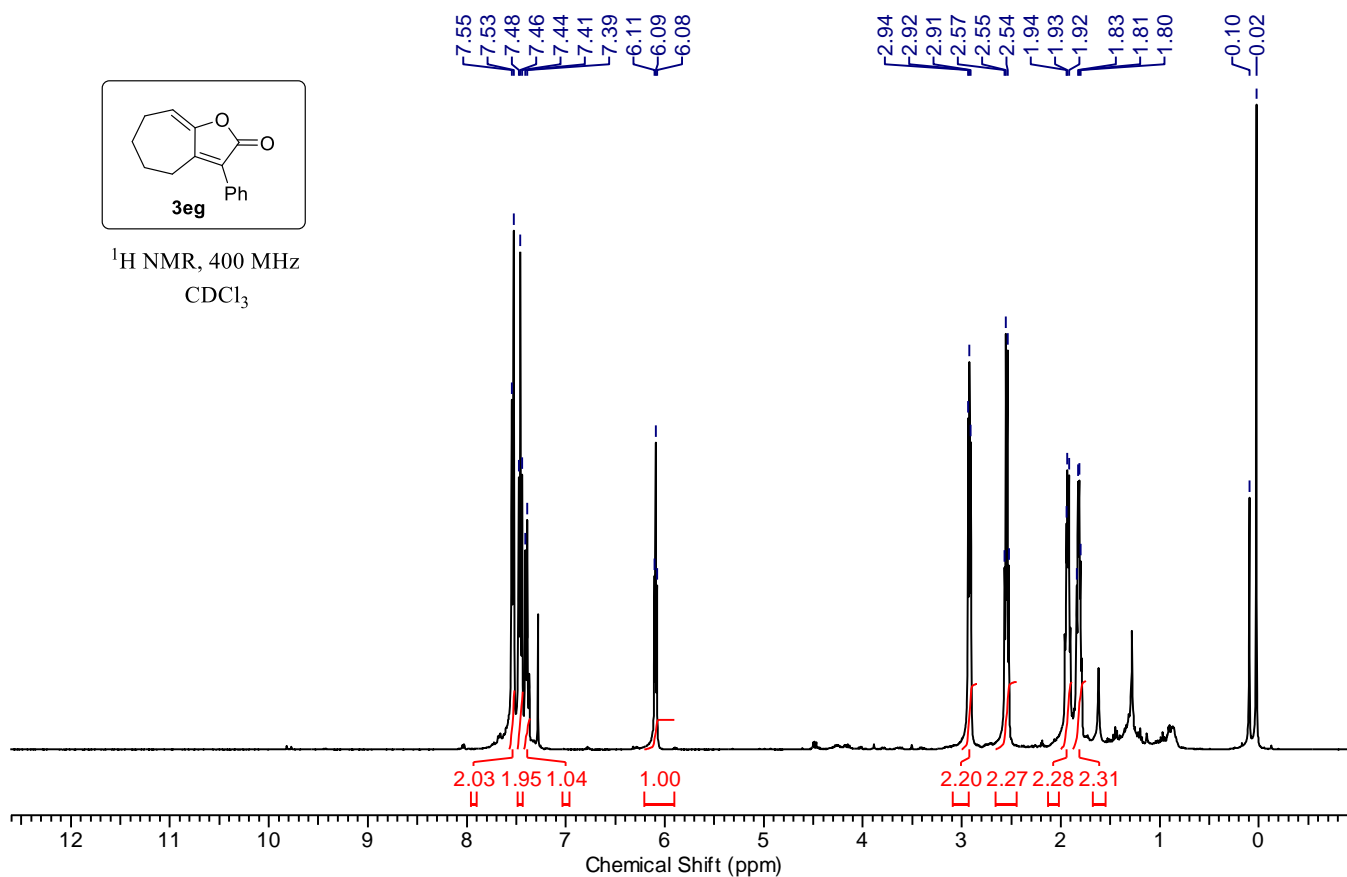
^{13}C NMR, 101 MHz
 CDCl_3



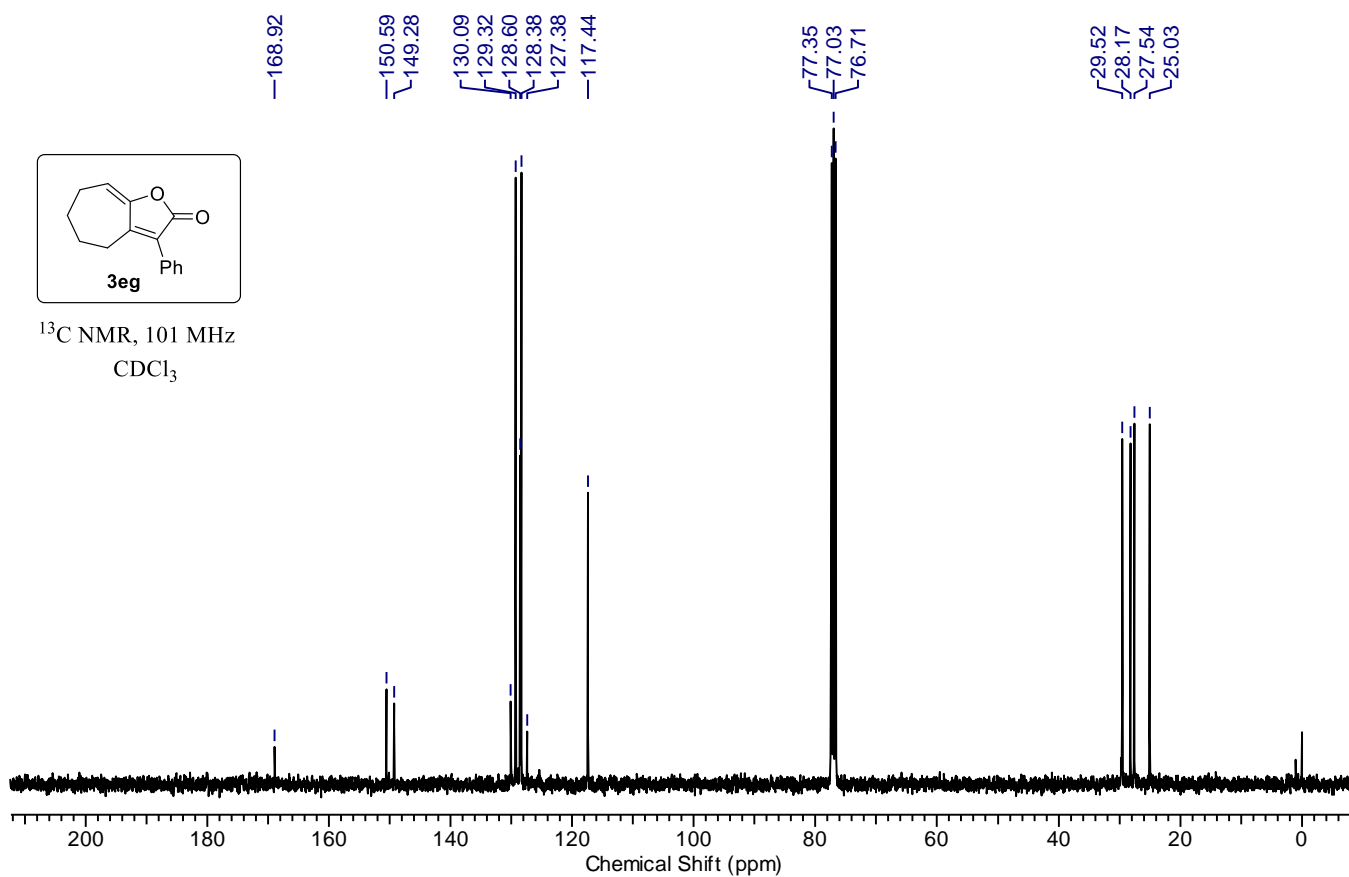
3-Phenyl-4,5,6,7-tetrahydro-2H-cyclohepta[b]-2-one (3eg):



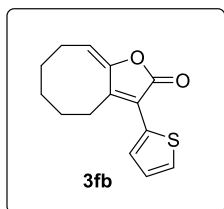
¹H NMR, 400 MHz
CDCl₃



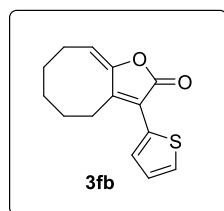
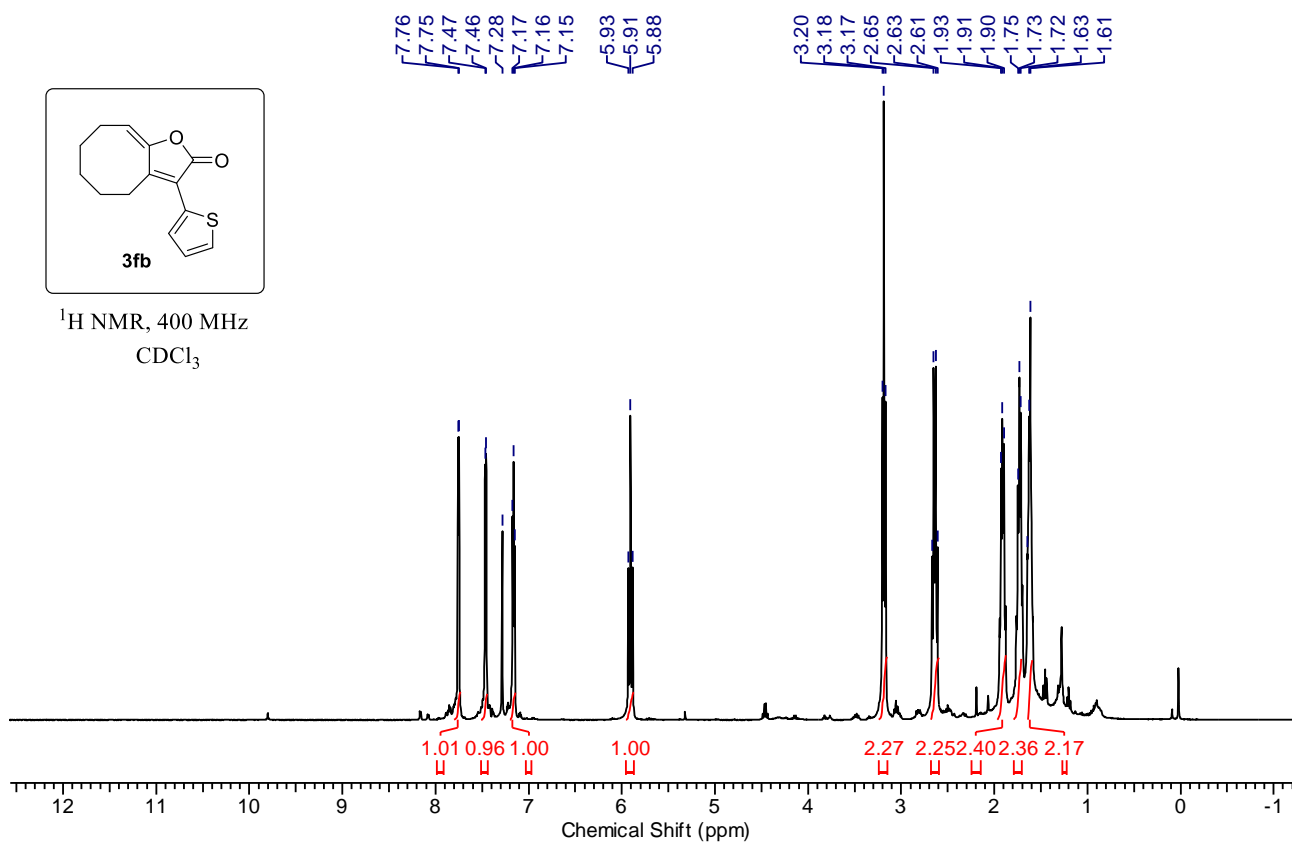
¹³C NMR, 101 MHz
CDCl₃



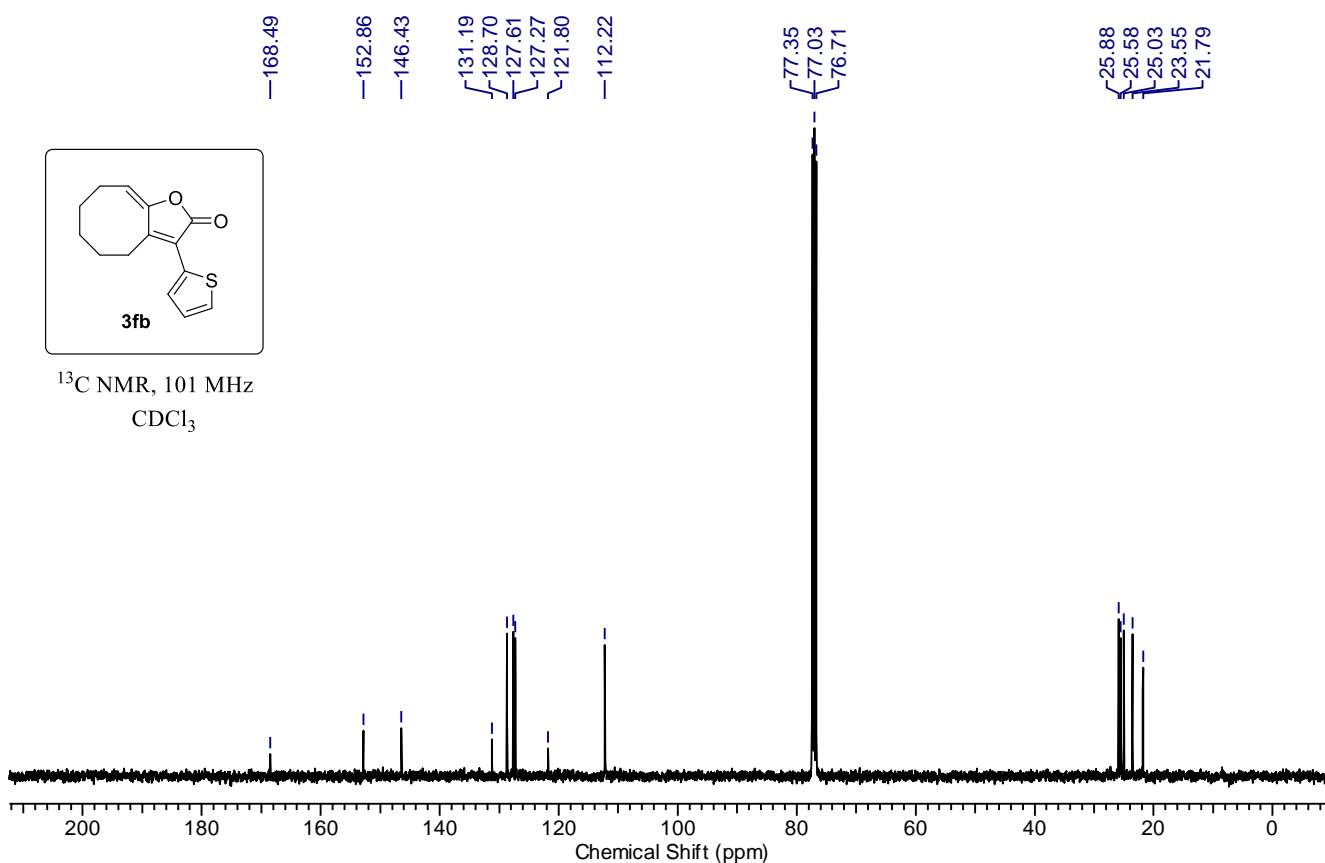
(E)-3-(Thiophen-2-yl)-5,6,7,8-tetrahydrocycloocta[b]furan-2(4H)-one (3fb):



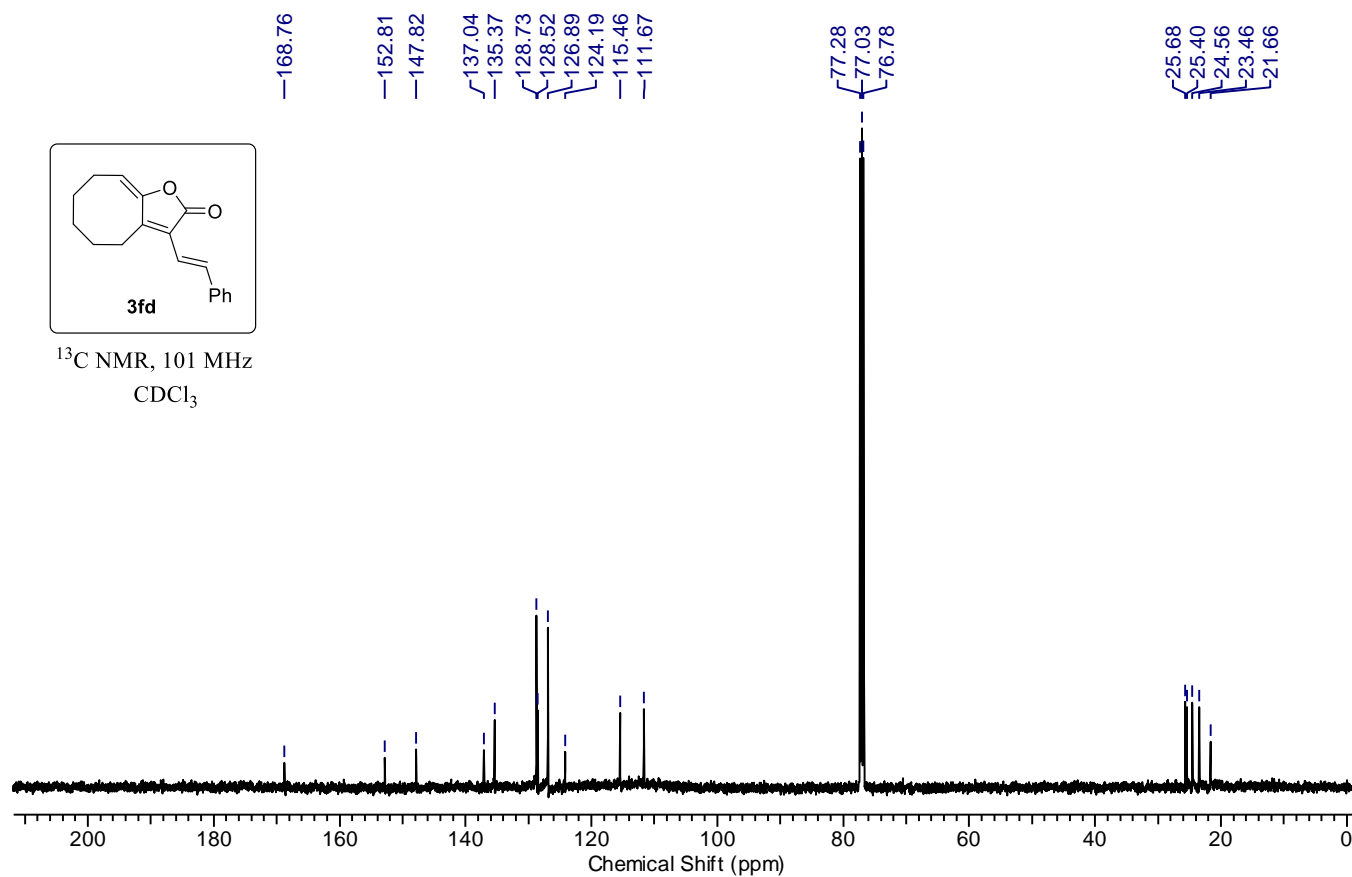
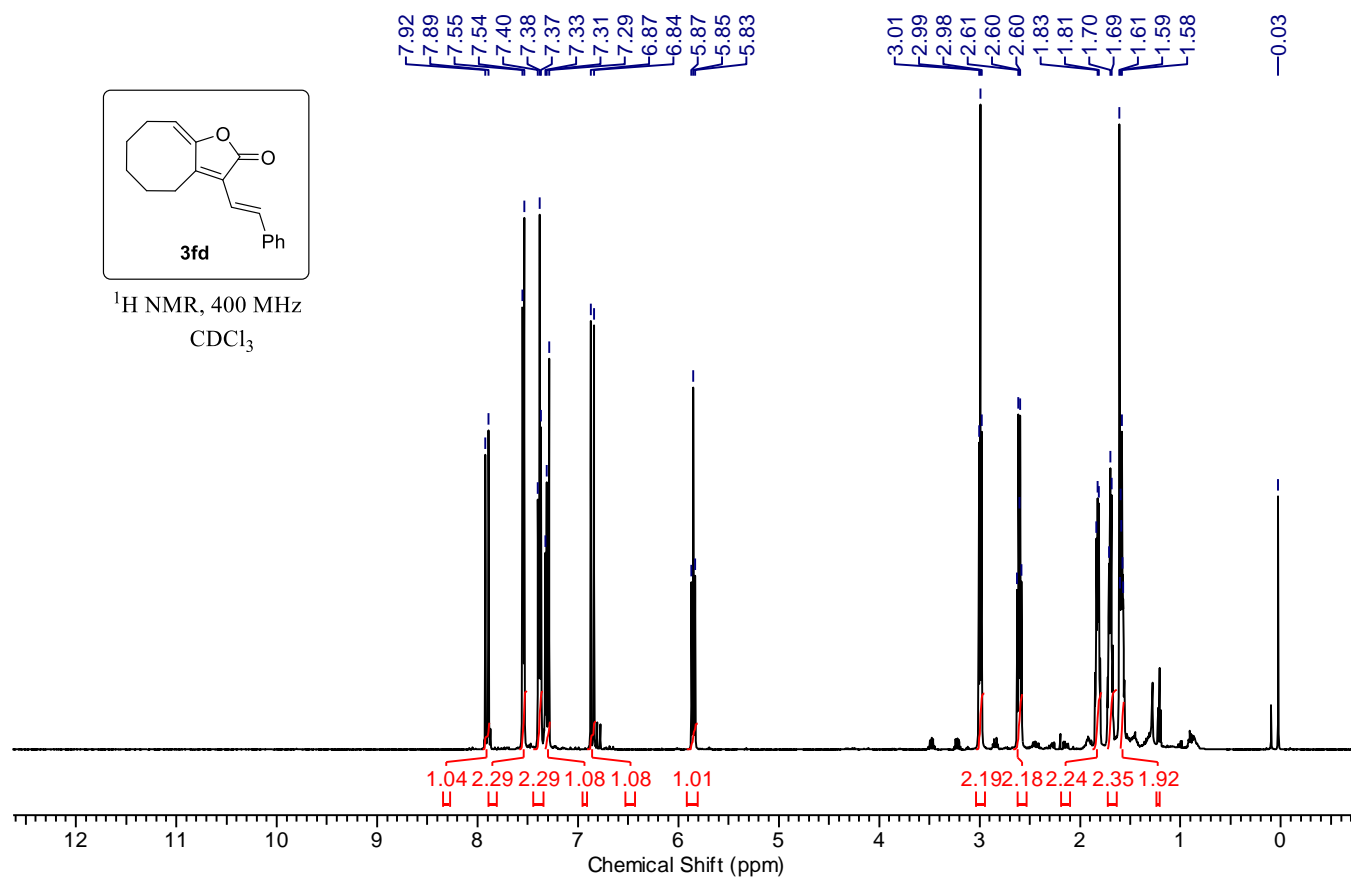
¹H NMR, 400 MHz
CDCl₃



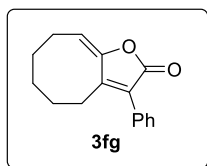
¹³C NMR, 101 MHz
CDCl₃



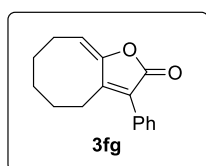
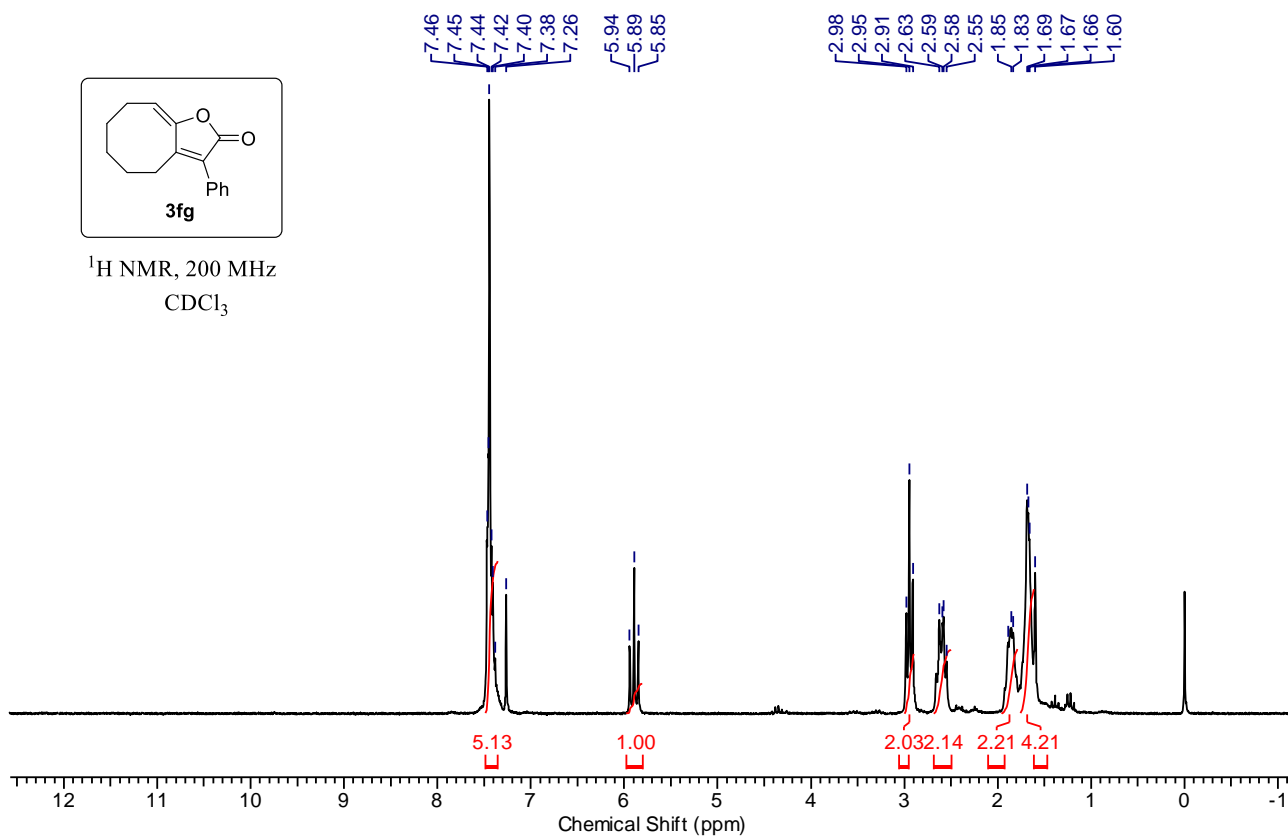
(E)-3-((E)-Styryl)-5,6,7,8-tetrahydrocycloocta[b]furan-2(4H)-one (3fd):



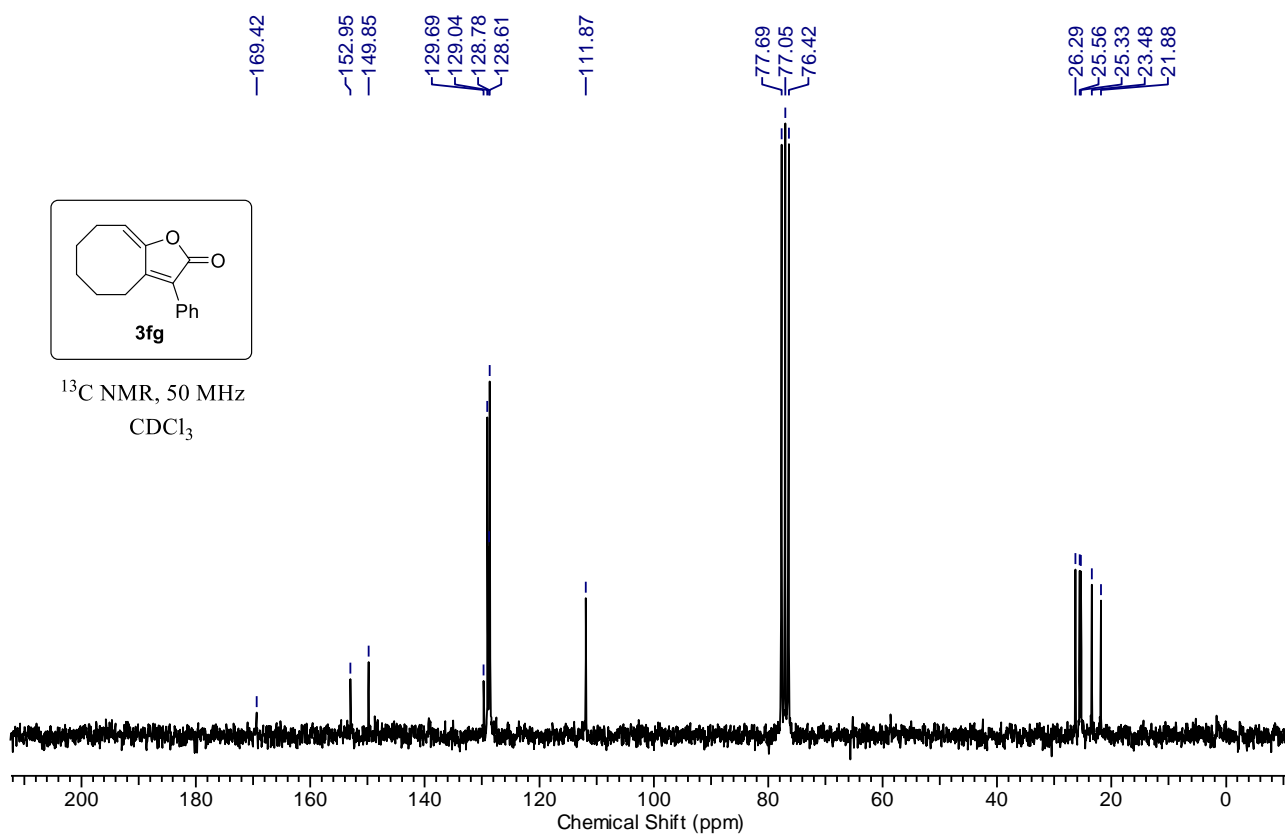
(E)-3-Phenyl-5,6,7,8-tetrahydrocycloocta[b]furan-2(4H)-one (3fg):



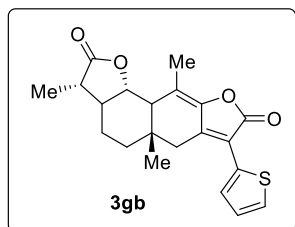
¹H NMR, 200 MHz
CDCl₃



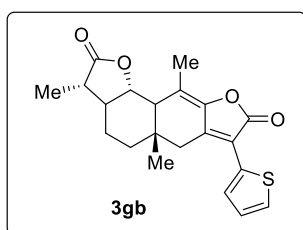
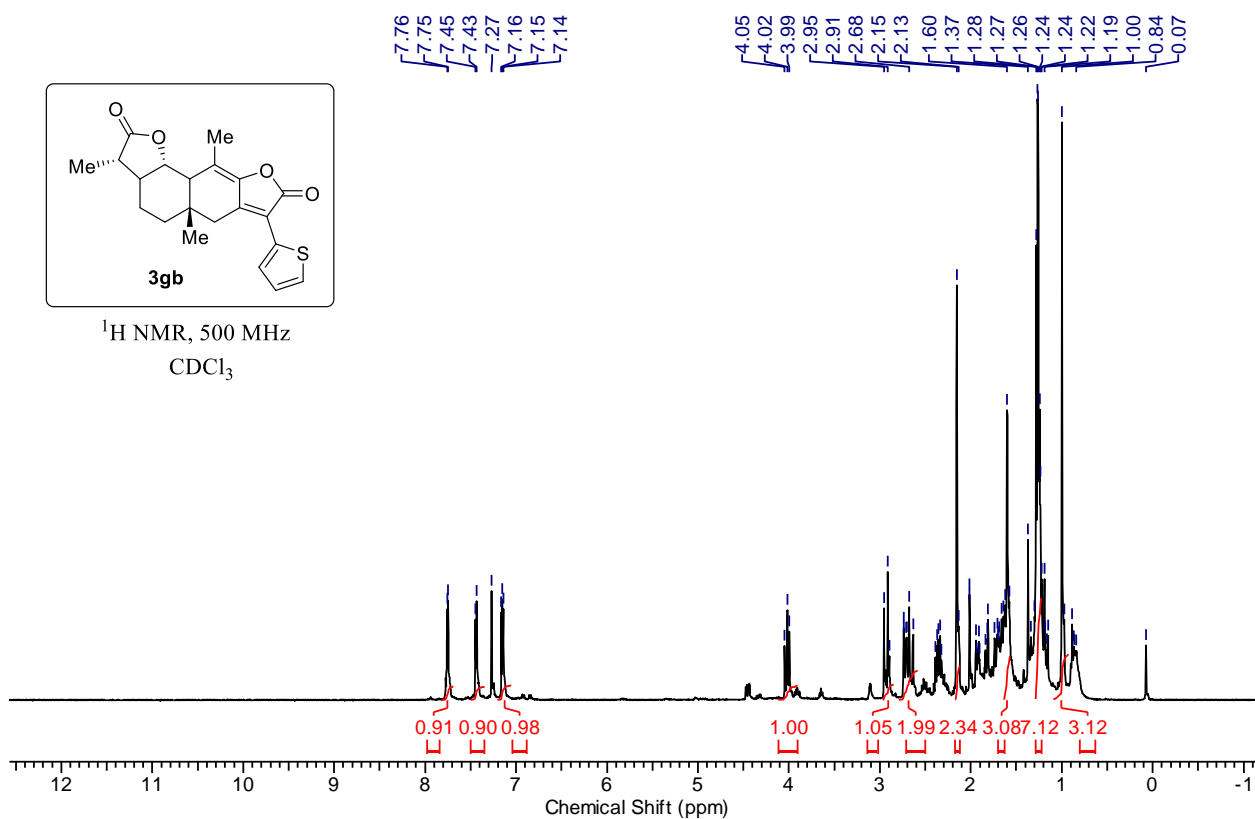
¹³C NMR, 50 MHz
CDCl₃



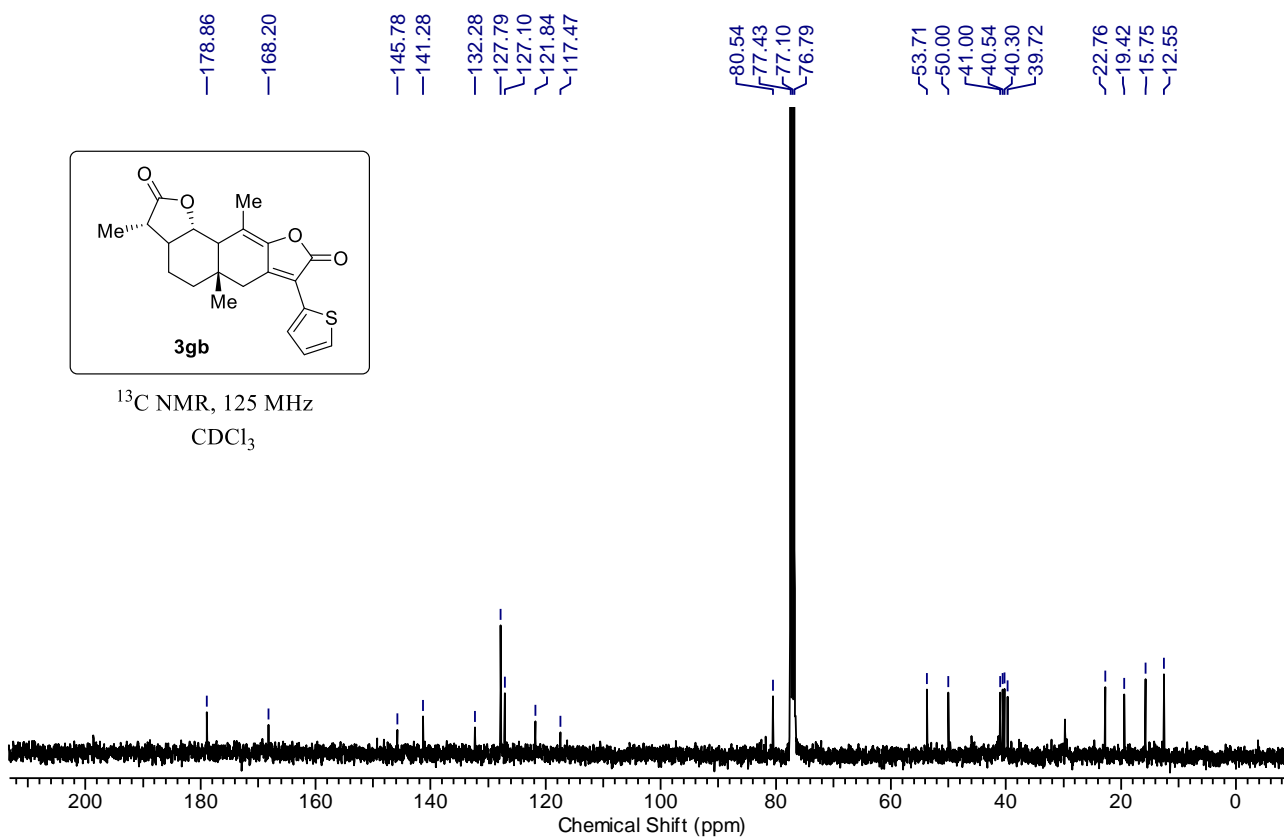
(3*S*,5*aS*,10*bS*)-3,5*a*,10-trimethyl-7-(thiophen-2-yl)-3,3*a*,4,5,5*a*,6,10*a*,10*b*-octahydronaphtho[1,2-*b*:7,6-*b'*]difuran-2,8-dione (3*gb*):



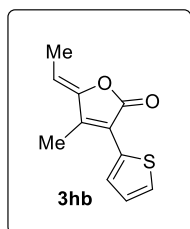
¹H NMR, 500 MHz
CDCl₃



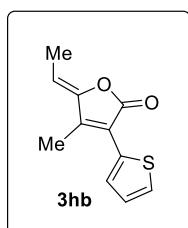
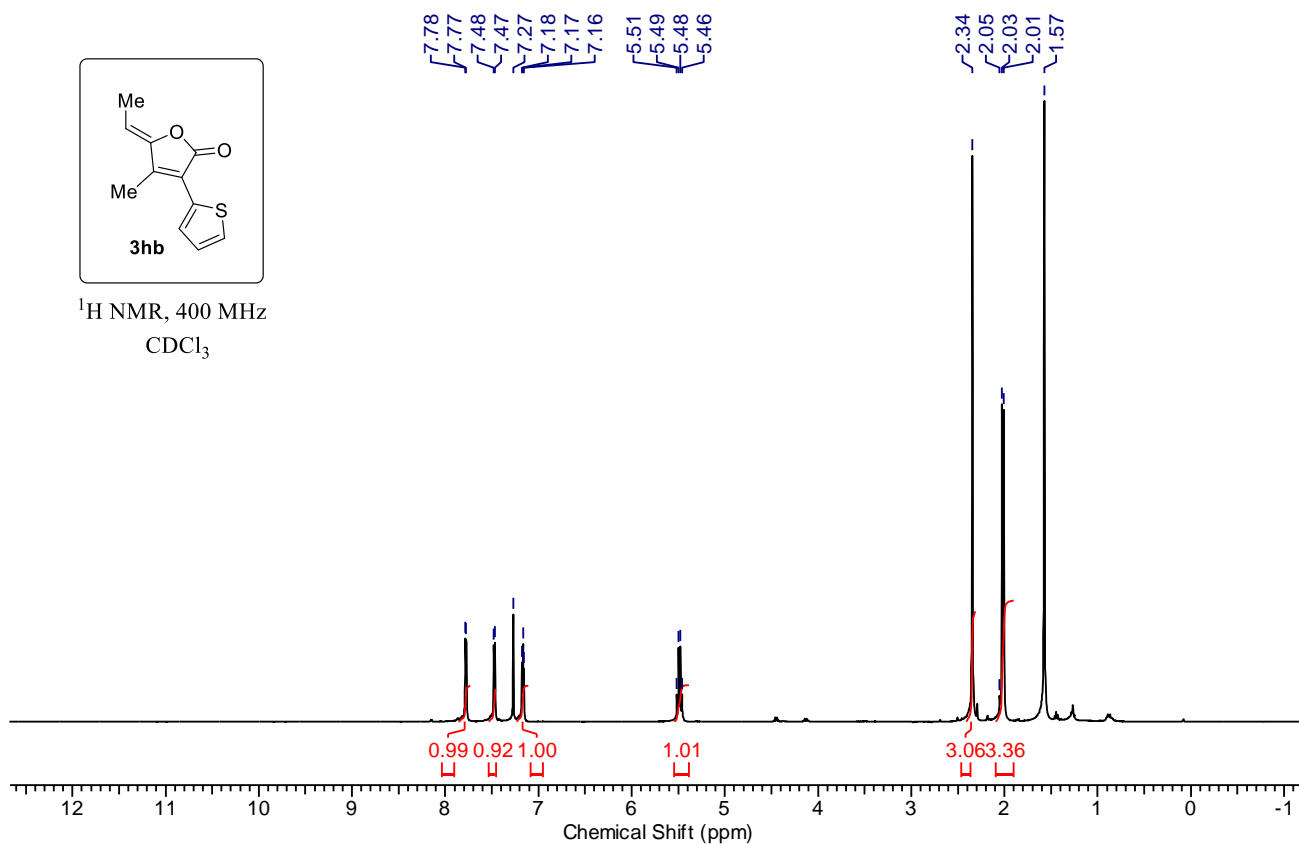
¹³C NMR, 125 MHz
CDCl₃



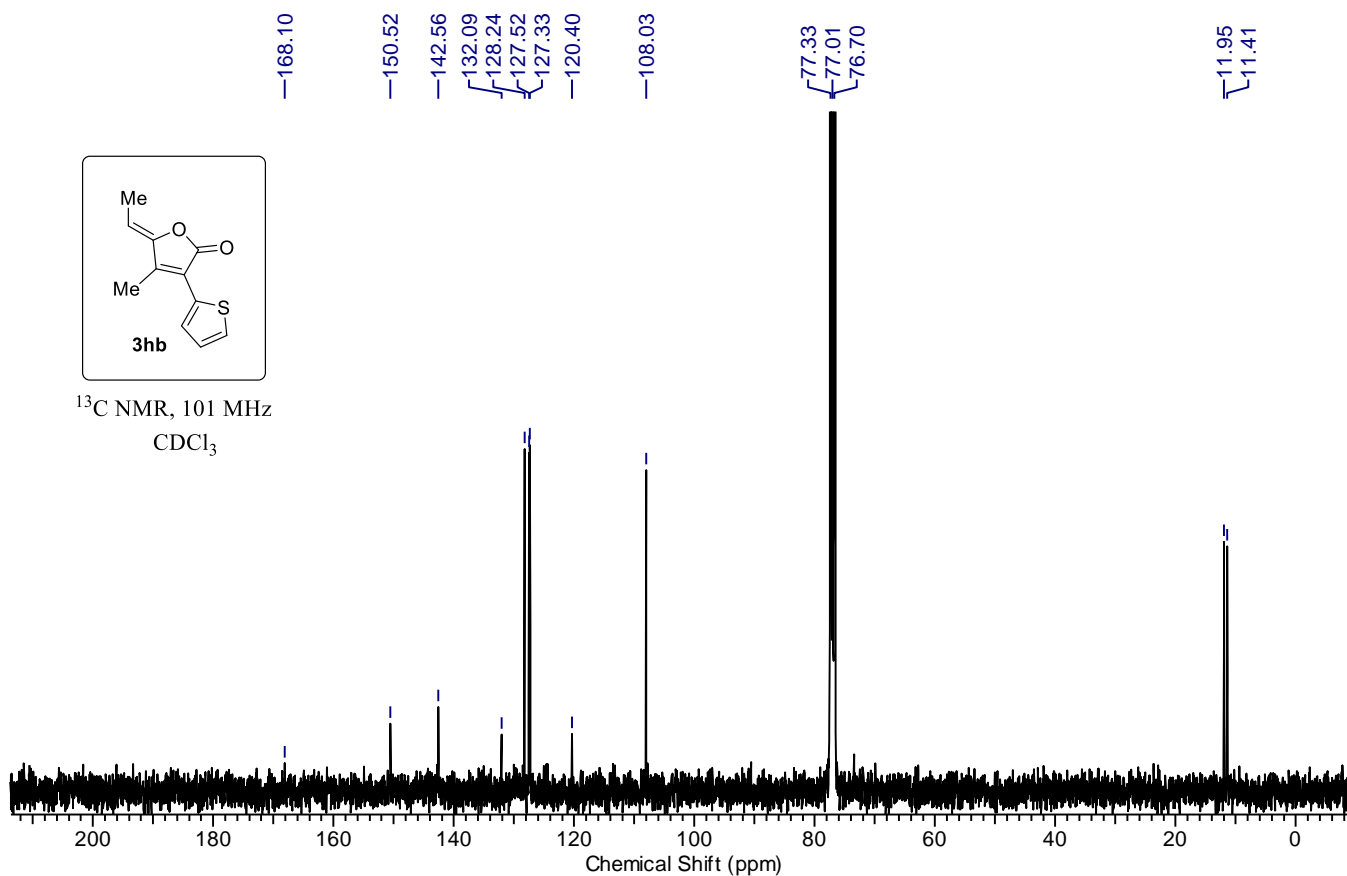
(Z)-5-Ethylidene-4-methyl-3-(thiophen-2-yl)furan-2(5H)-one (3hb):



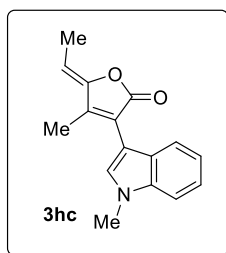
$^1\text{H NMR}$, 400 MHz
 CDCl_3



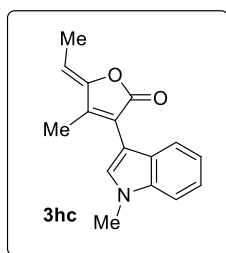
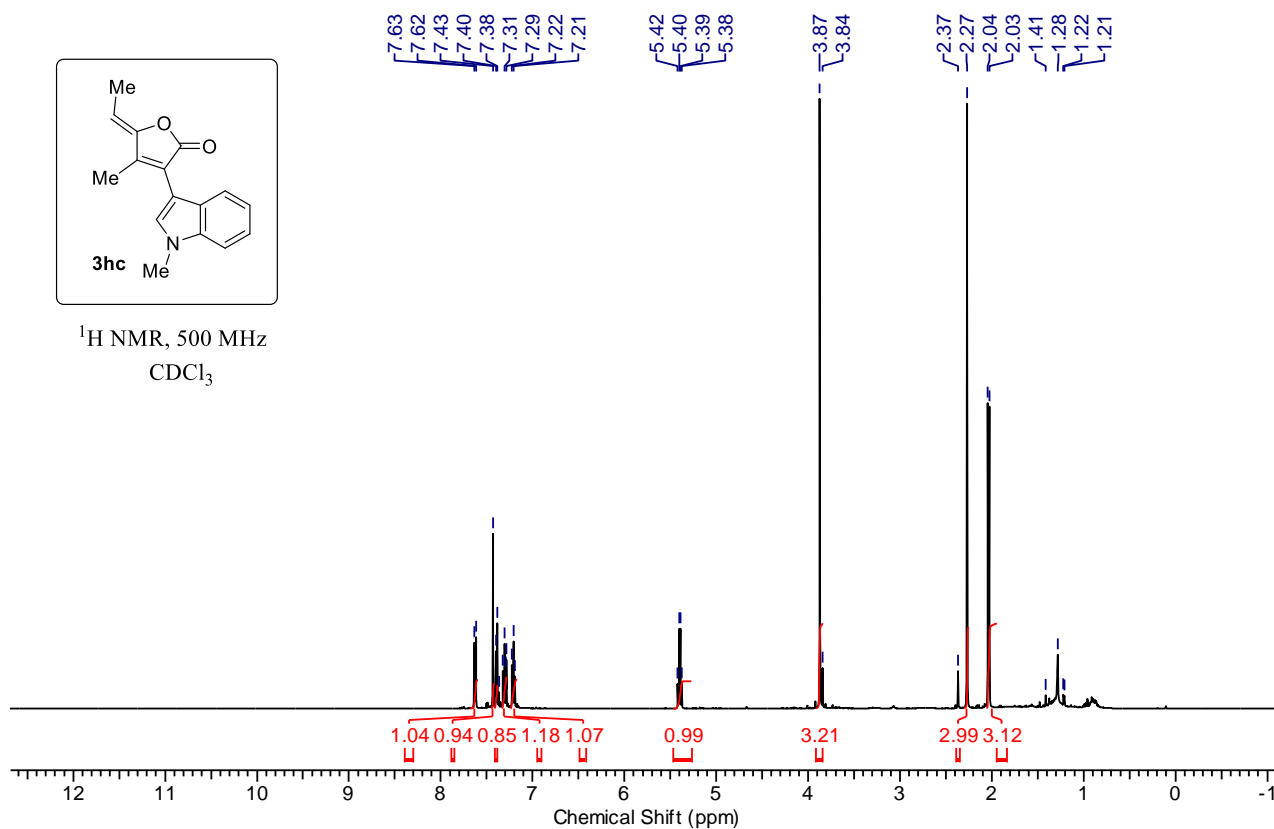
$^{13}\text{C NMR}$, 101 MHz
 CDCl_3



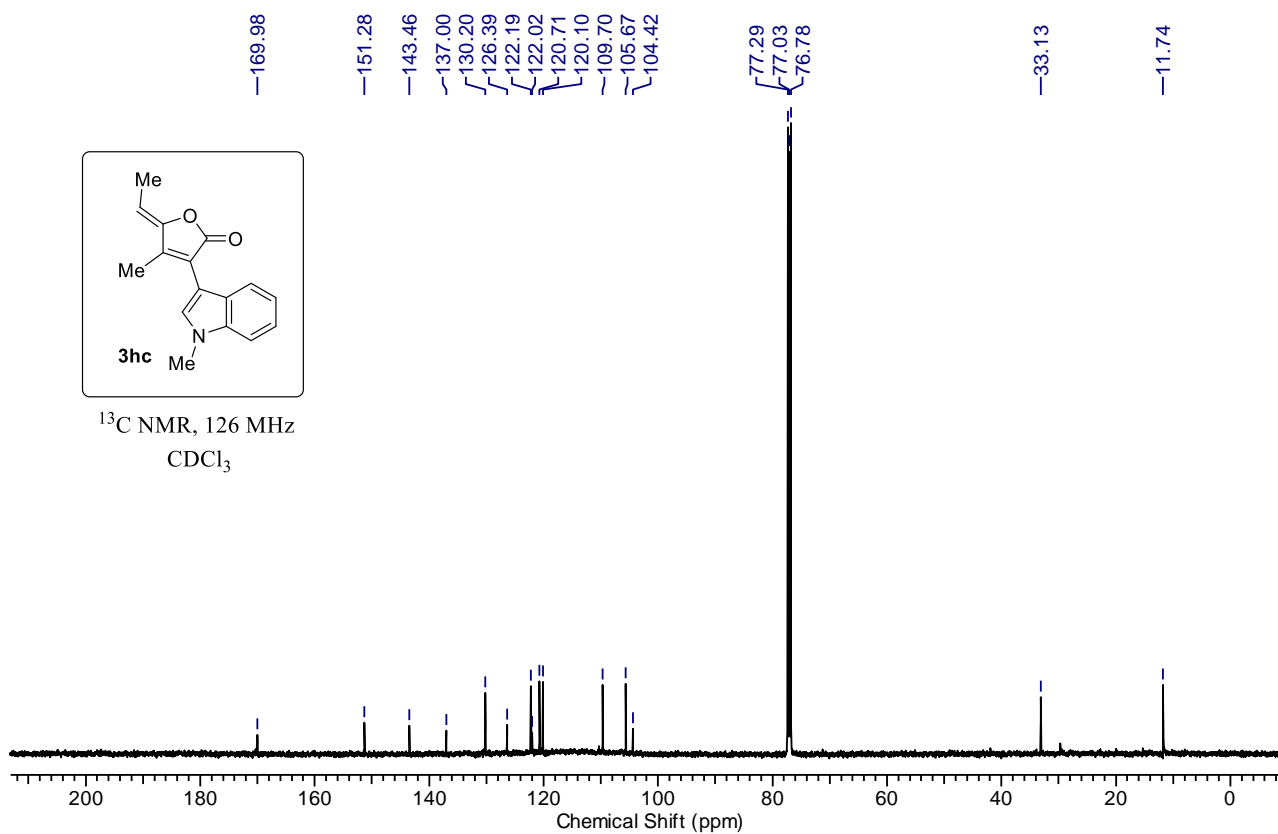
(Z)-5-Ethylidene-4-methyl-3-(1-methyl-1H-indol-3-yl)furan-2(5H)-one (3hc):



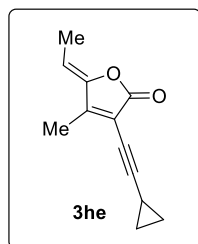
¹H NMR, 500 MHz
CDCl₃



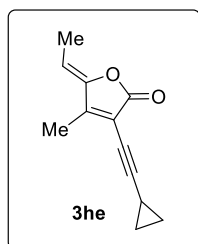
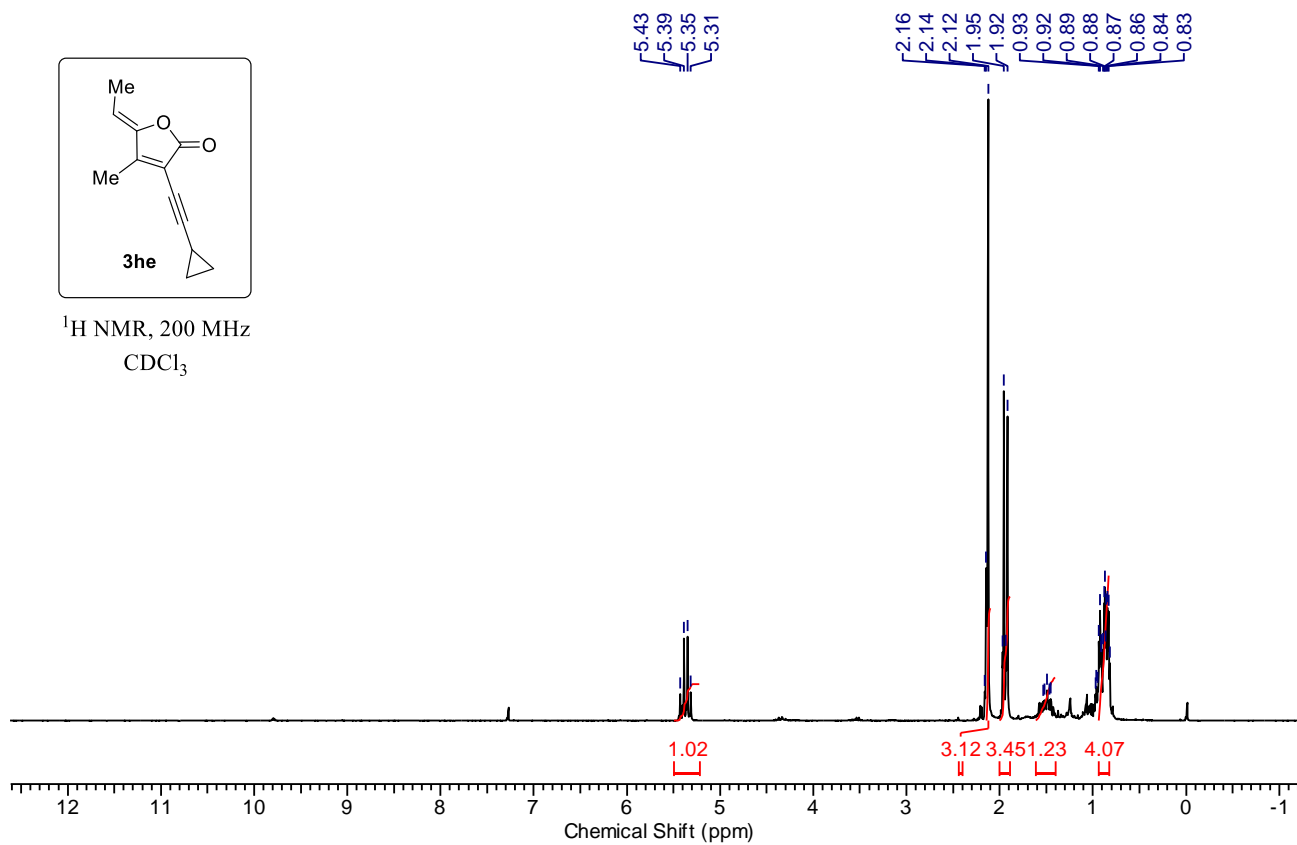
¹³C NMR, 126 MHz
CDCl₃



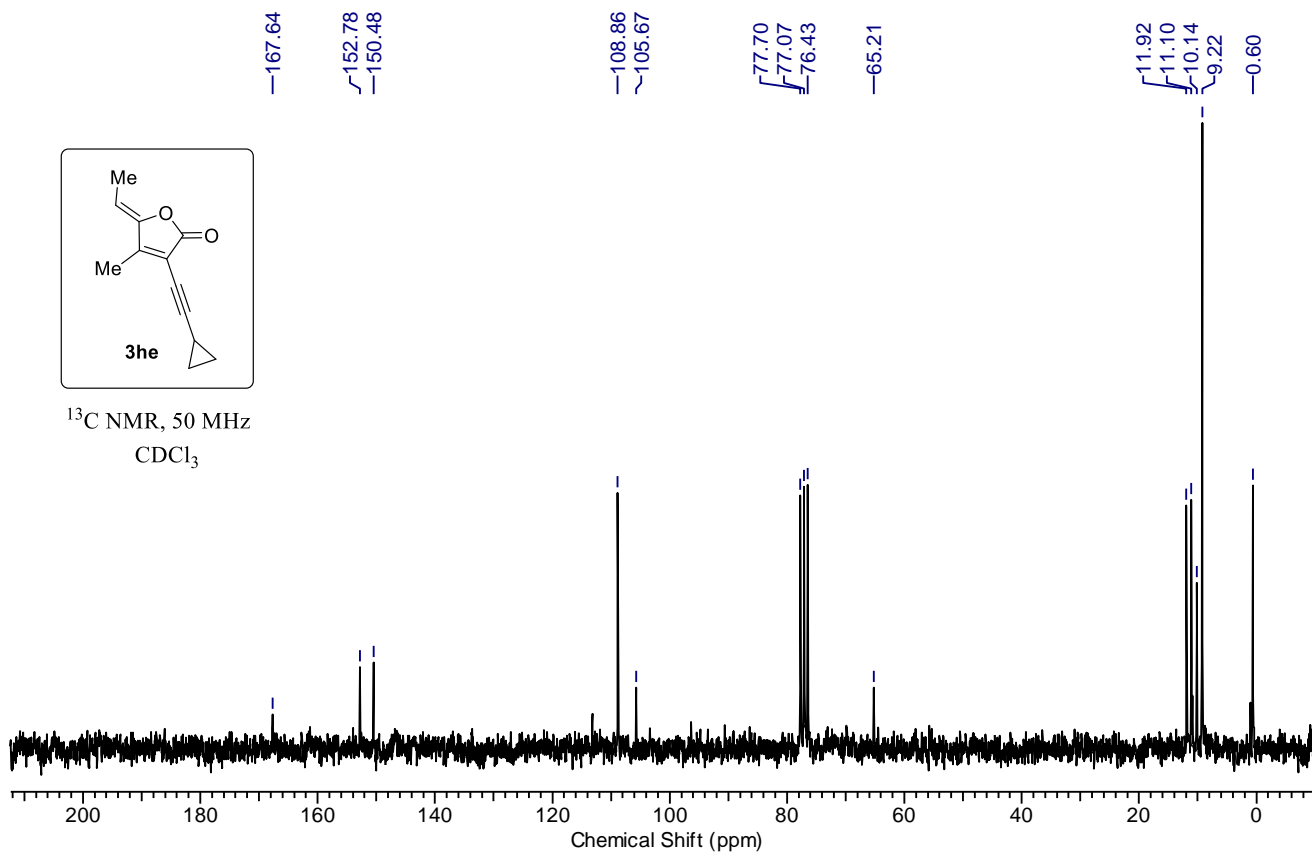
(Z)-3-(Cyclopropylethynyl)-5-ethylidene-4-methylfuran-2(5H)-one (3he):



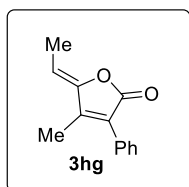
^1H NMR, 200 MHz
 CDCl_3



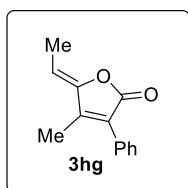
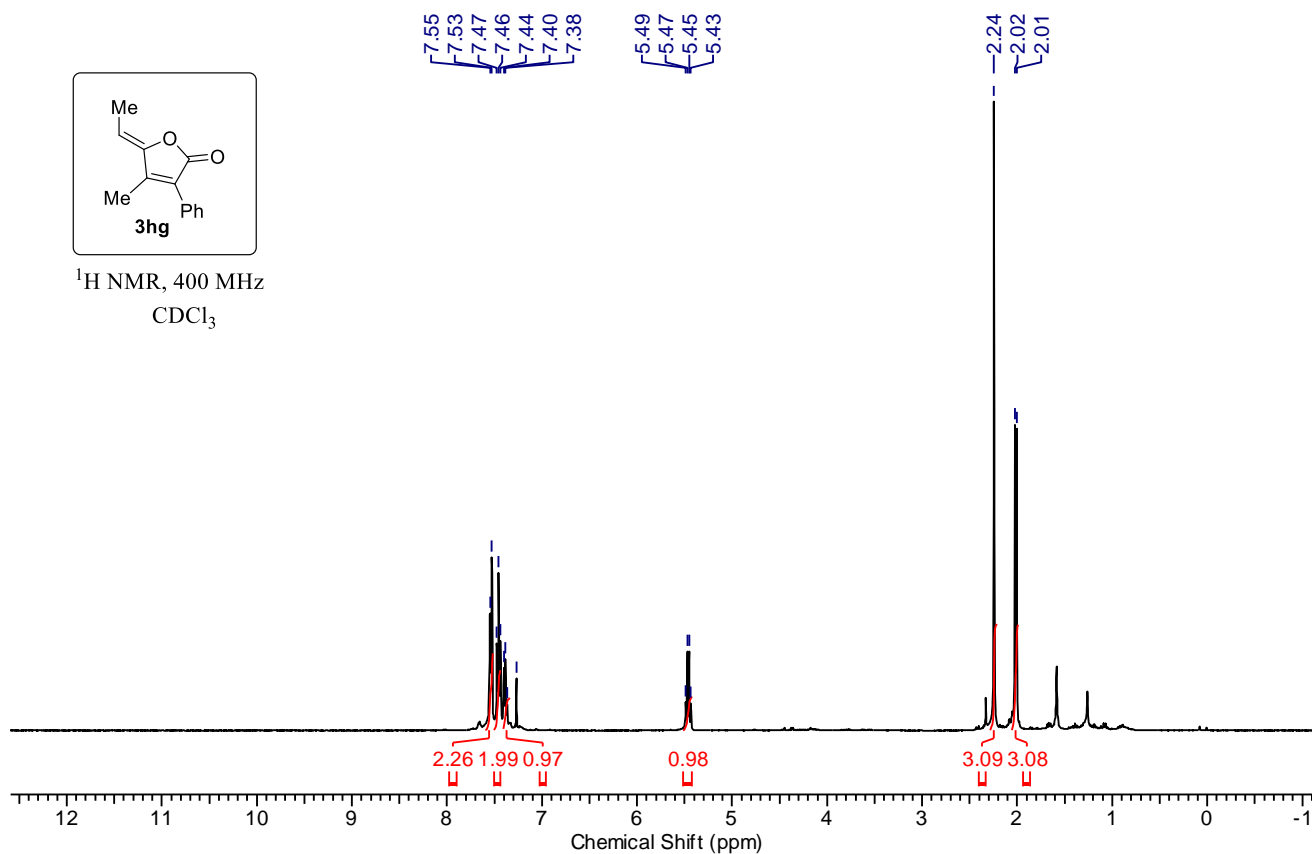
^{13}C NMR, 50 MHz
 CDCl_3



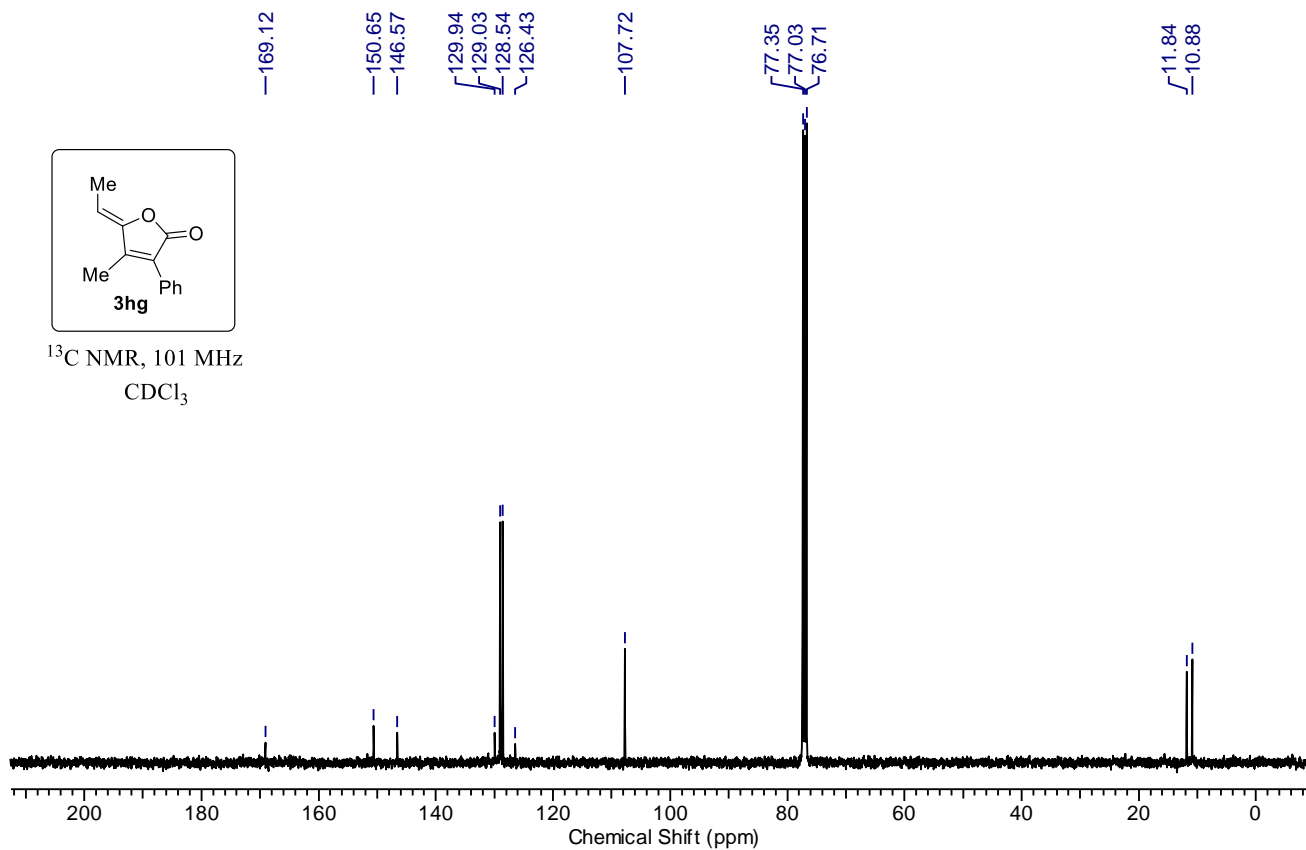
(Z)-Ethylidene-4-methyl-3-phenylfuran-2(5H)-one (3hg):



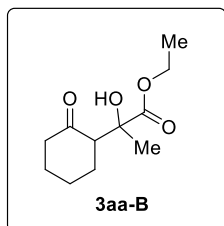
¹H NMR, 400 MHz
CDCl₃



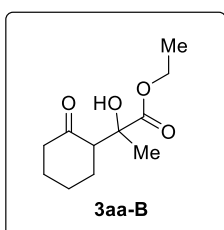
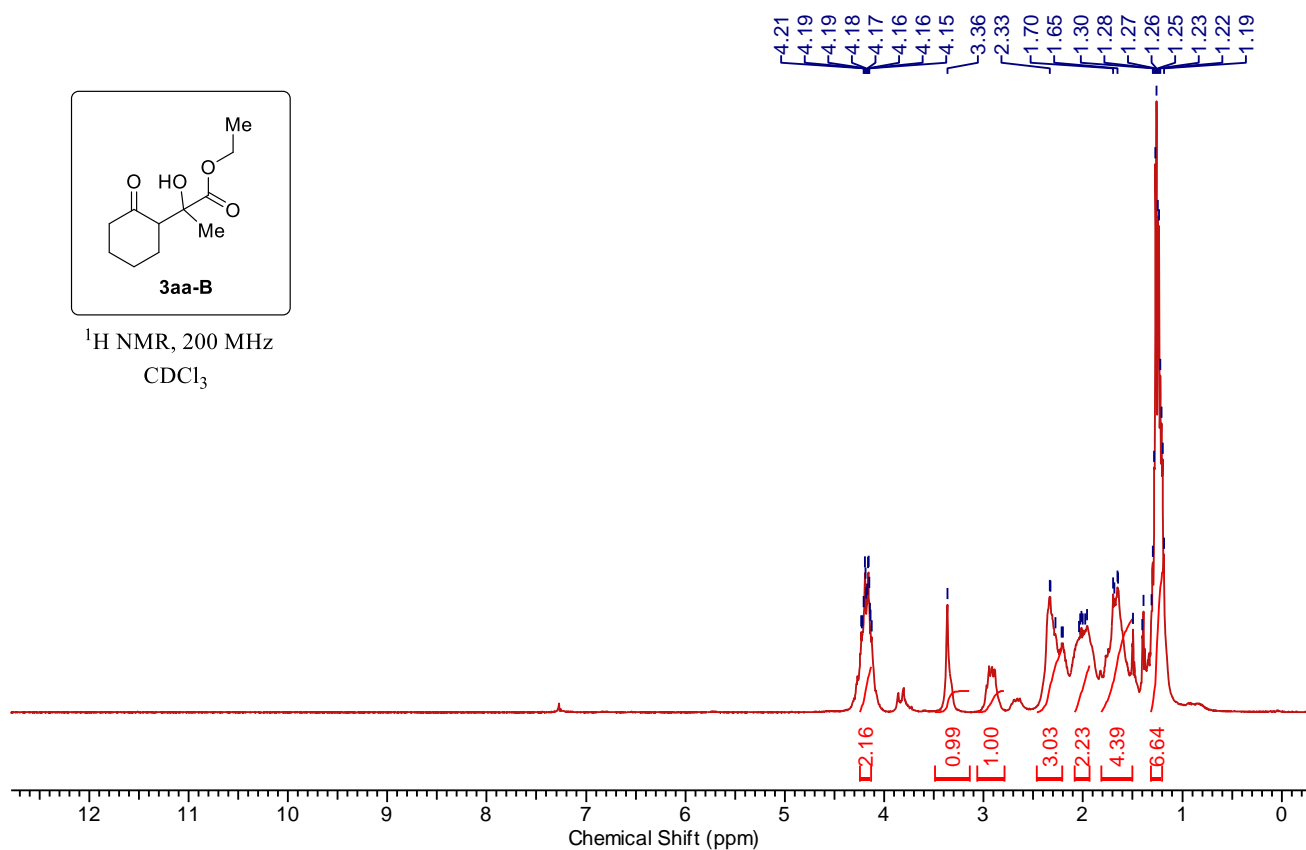
¹³C NMR, 101 MHz
CDCl₃



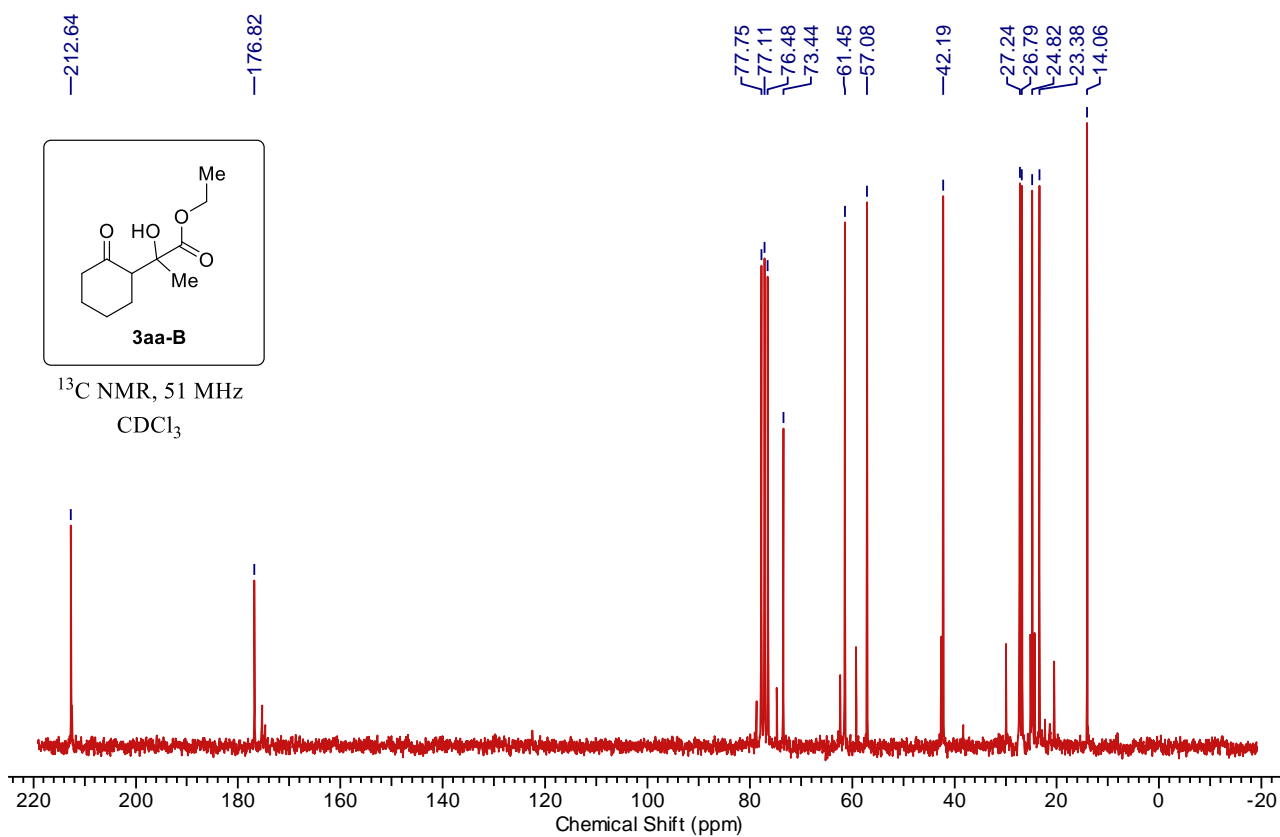
Ethyl 2-hydroxy-2-(2-oxocyclohexyl)propionate (3aa-B):



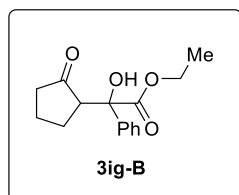
$^1\text{H NMR}$, 200 MHz
 CDCl_3



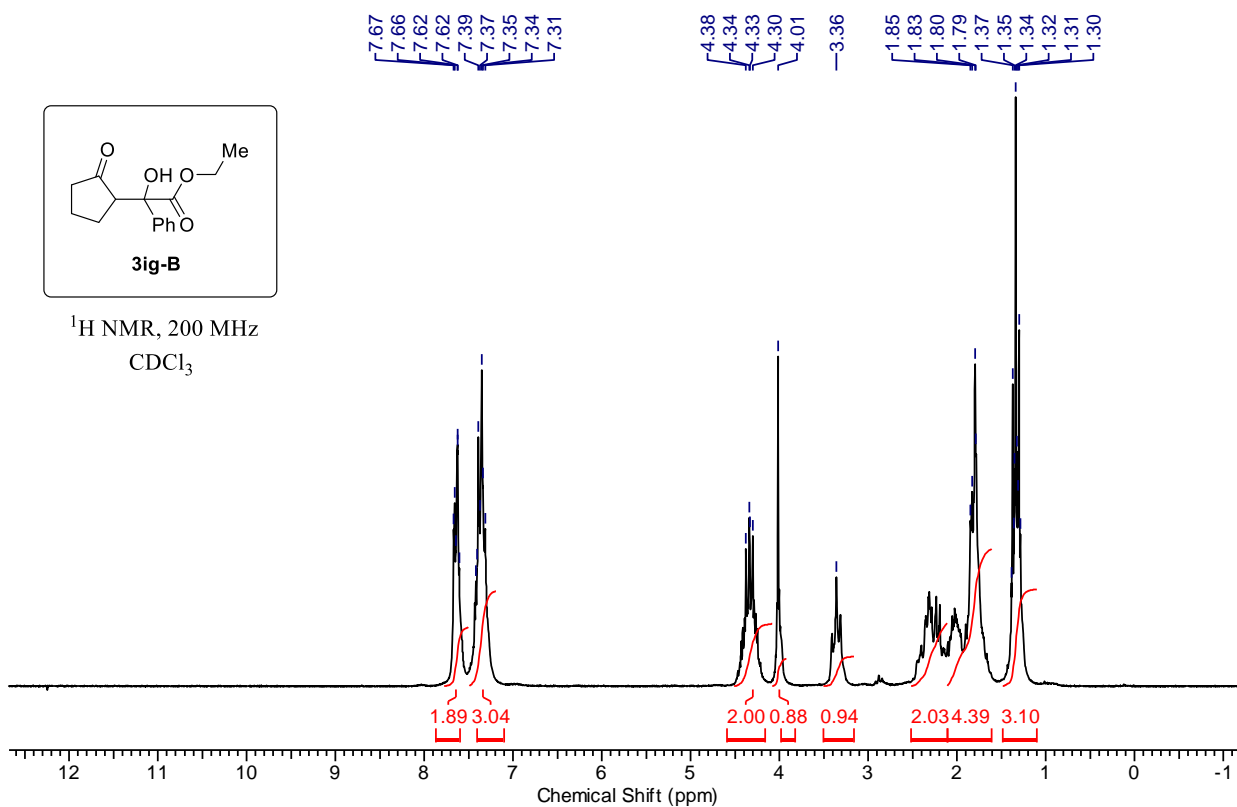
$^{13}\text{C NMR}$, 51 MHz
 CDCl_3



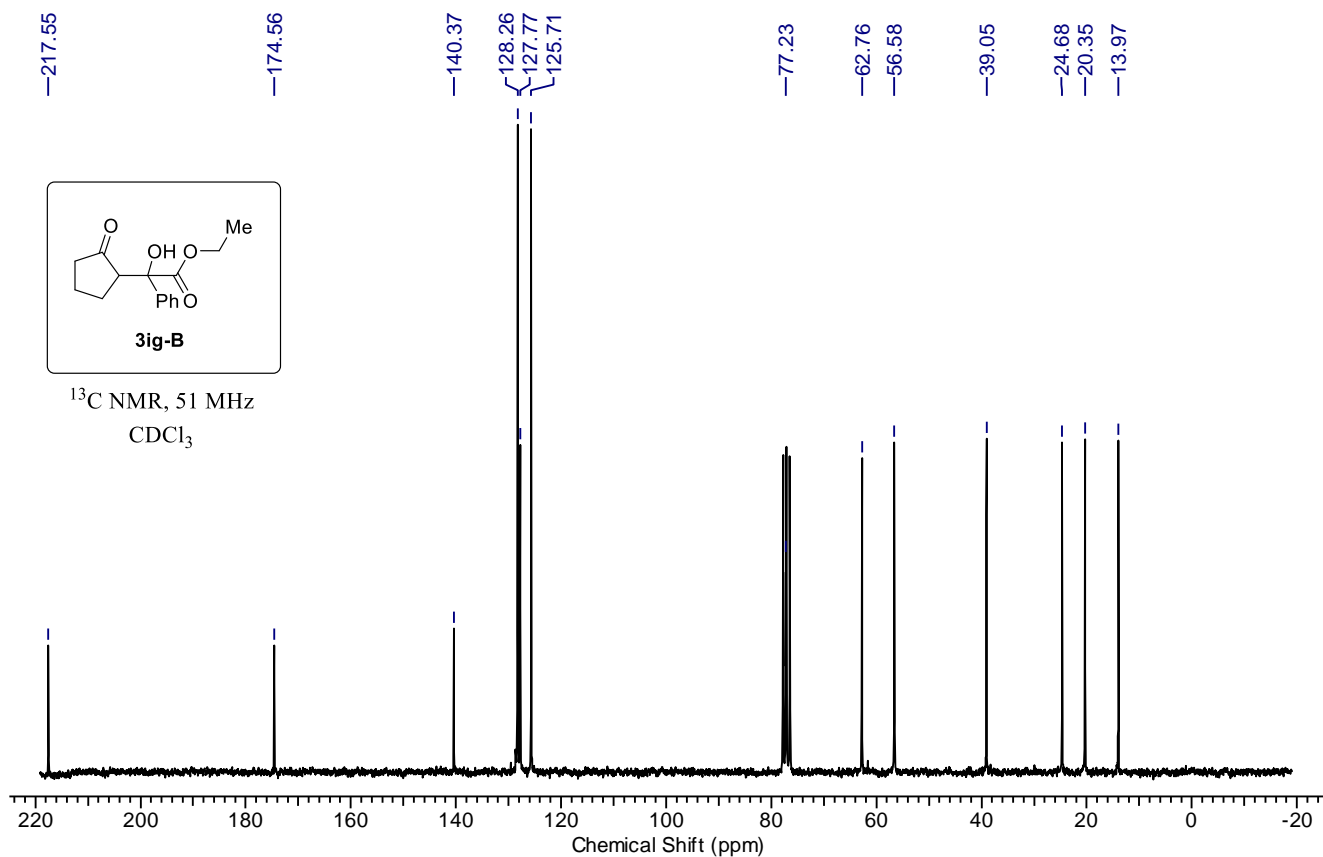
Ethyl 2-hydroxy-2-(2-oxocyclopentyl)-2-phenylacetate (**3ig-B**):



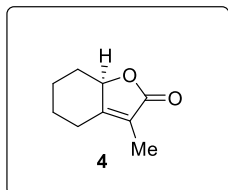
¹H NMR, 200 MHz
CDCl₃



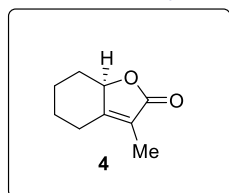
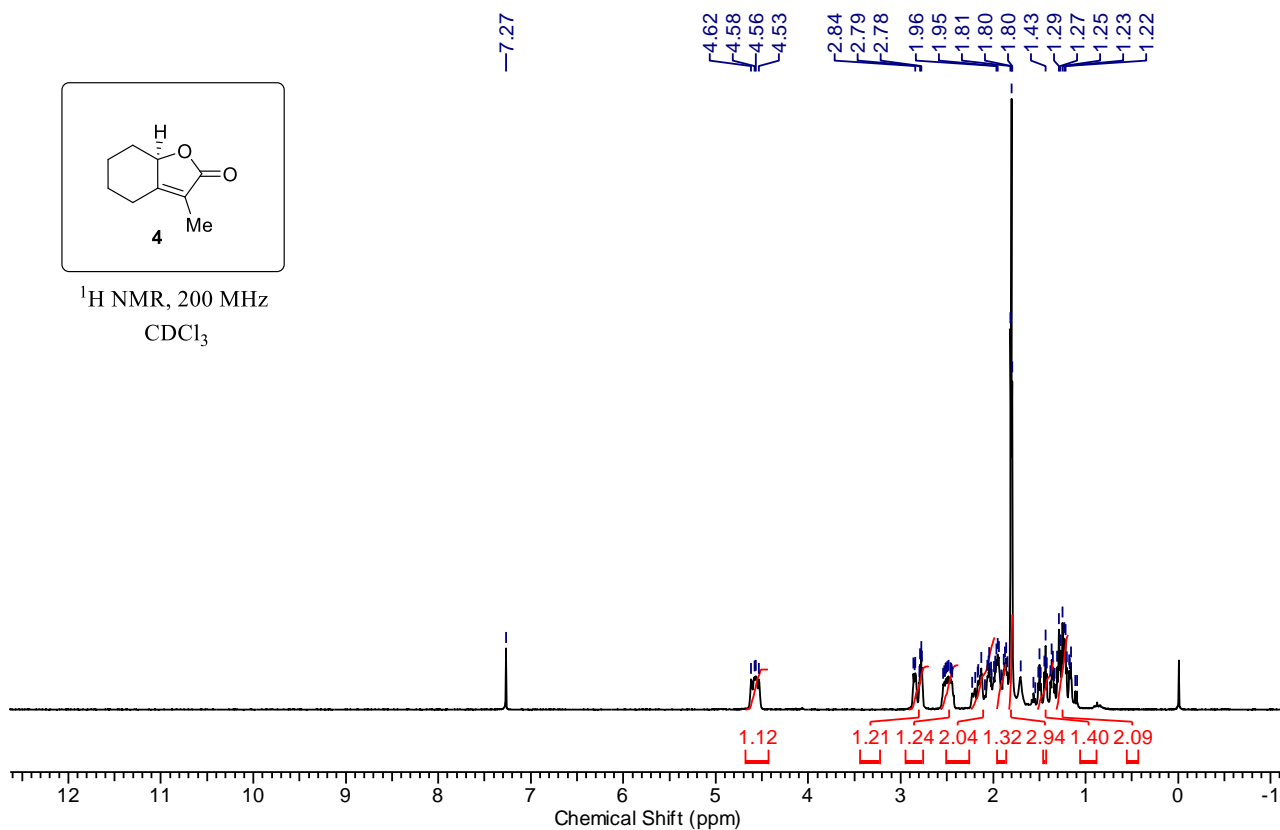
¹³C NMR, 51 MHz
CDCl₃



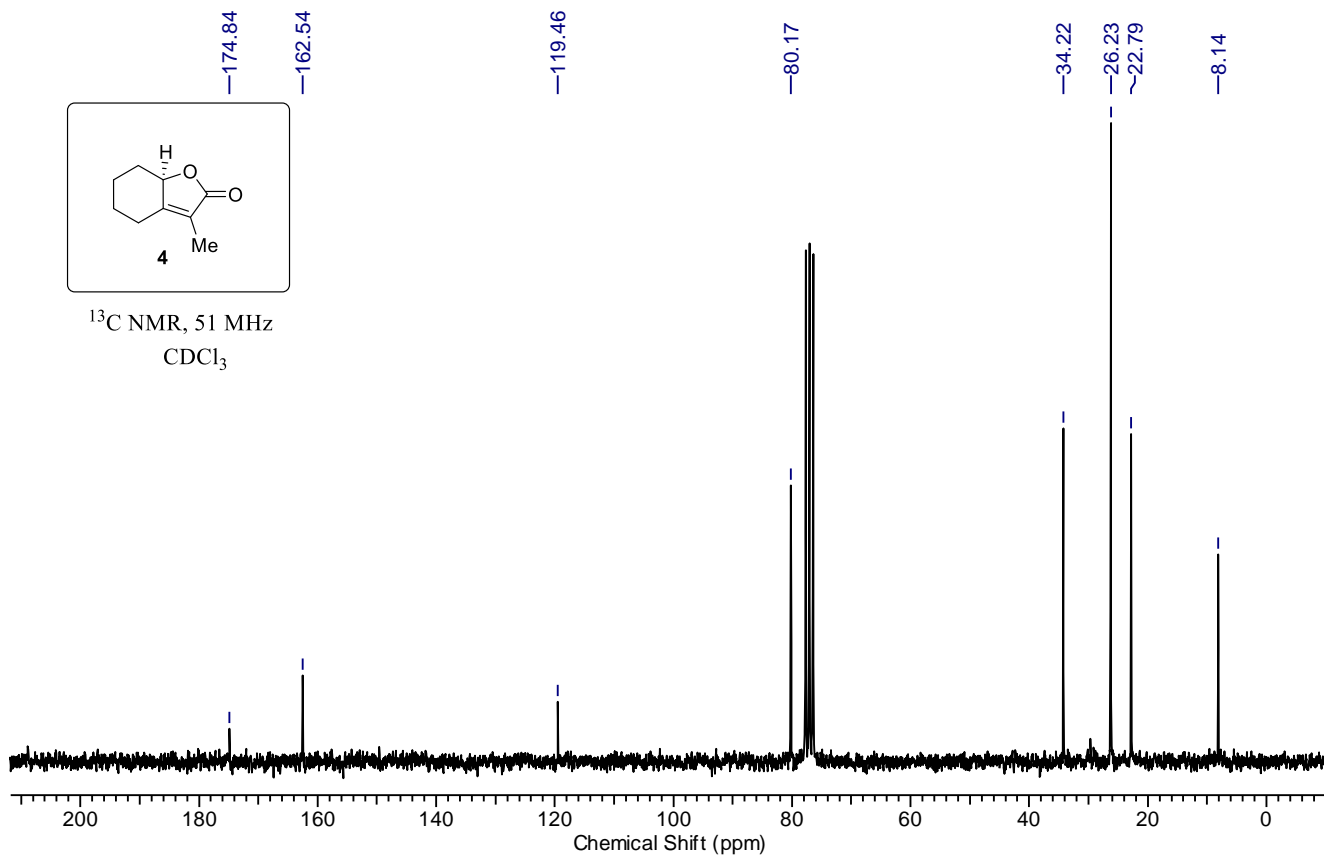
3-Methyl-5,6,7,7a-tetrahydrobenzofuran-2(4H)-one (4):



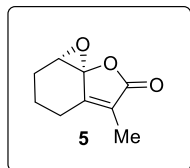
^1H NMR, 200 MHz
 CDCl_3



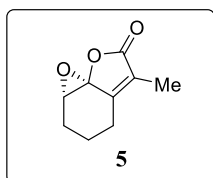
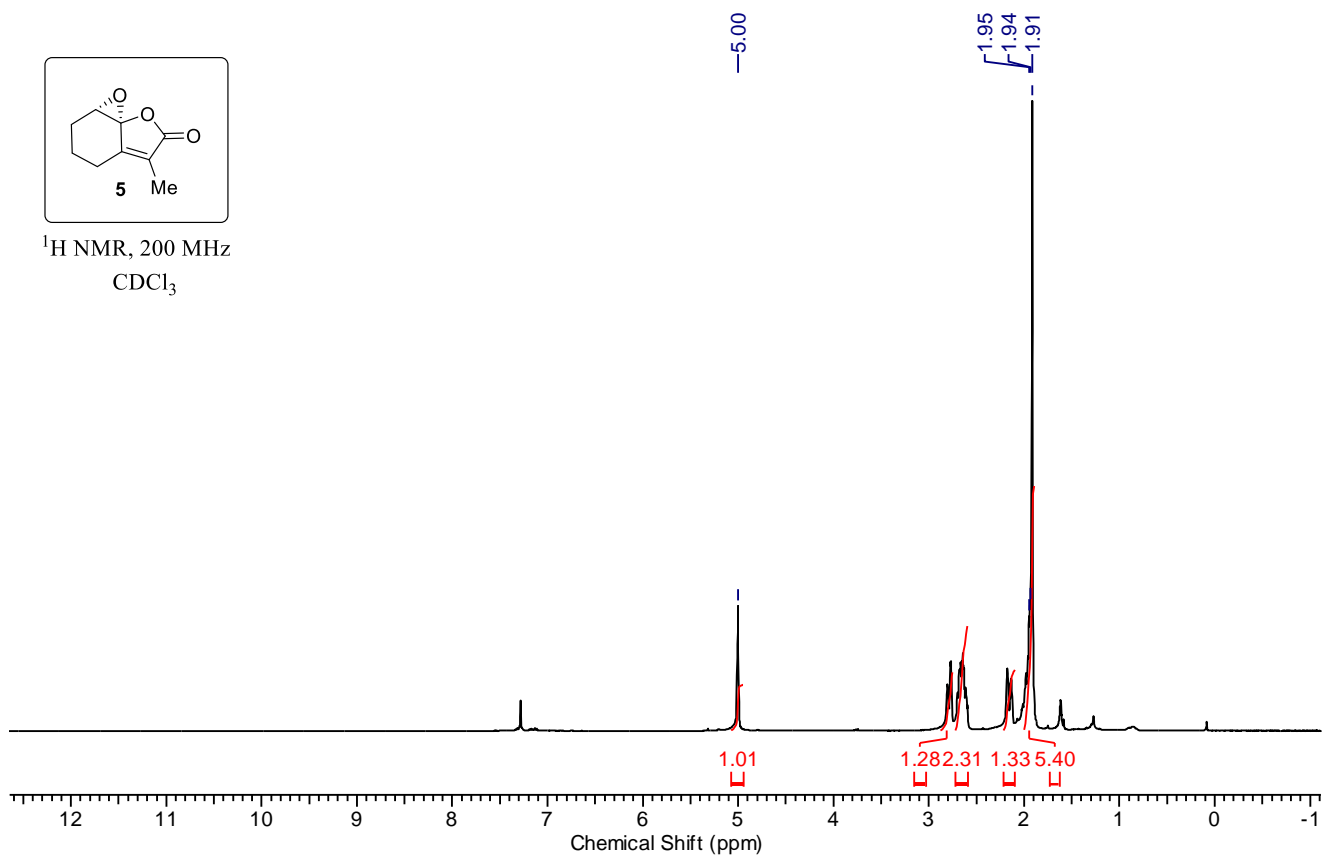
^{13}C NMR, 51 MHz
 CDCl_3



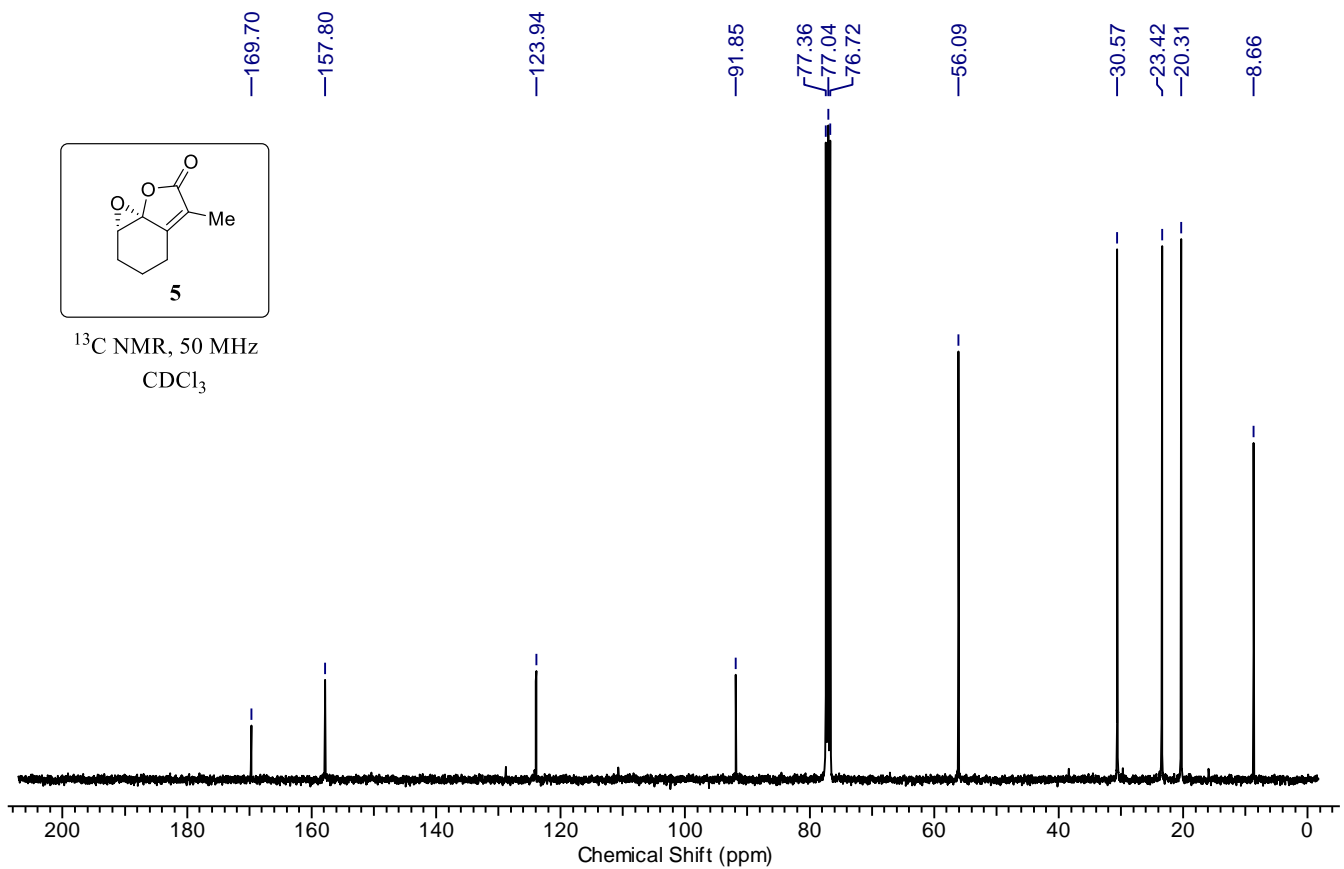
5-Methyl-3,4-dihydro-2aH-oxireno[2,3-h]benzofuran-6(2H)-one (5):

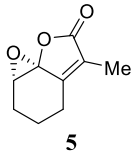


¹H NMR, 200 MHz
CDCl₃

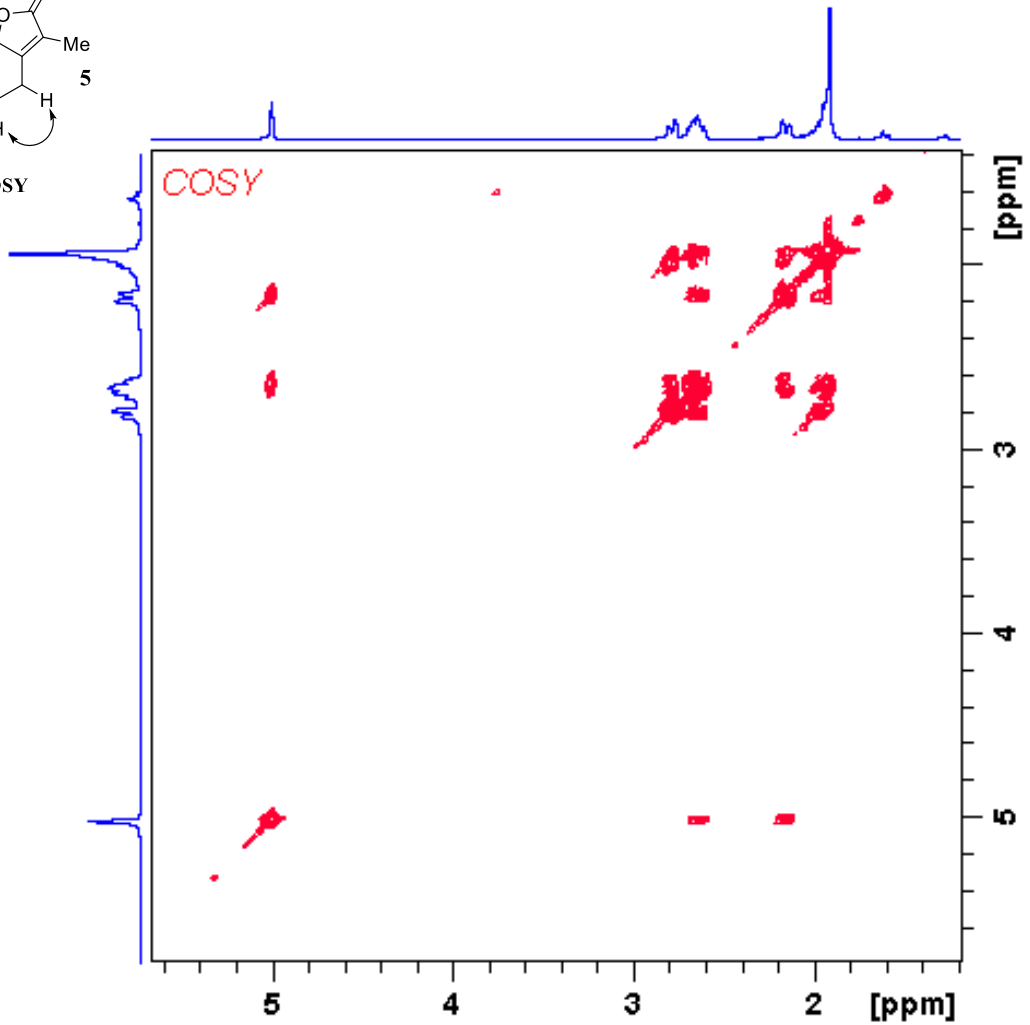
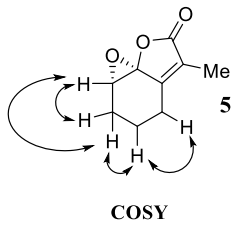
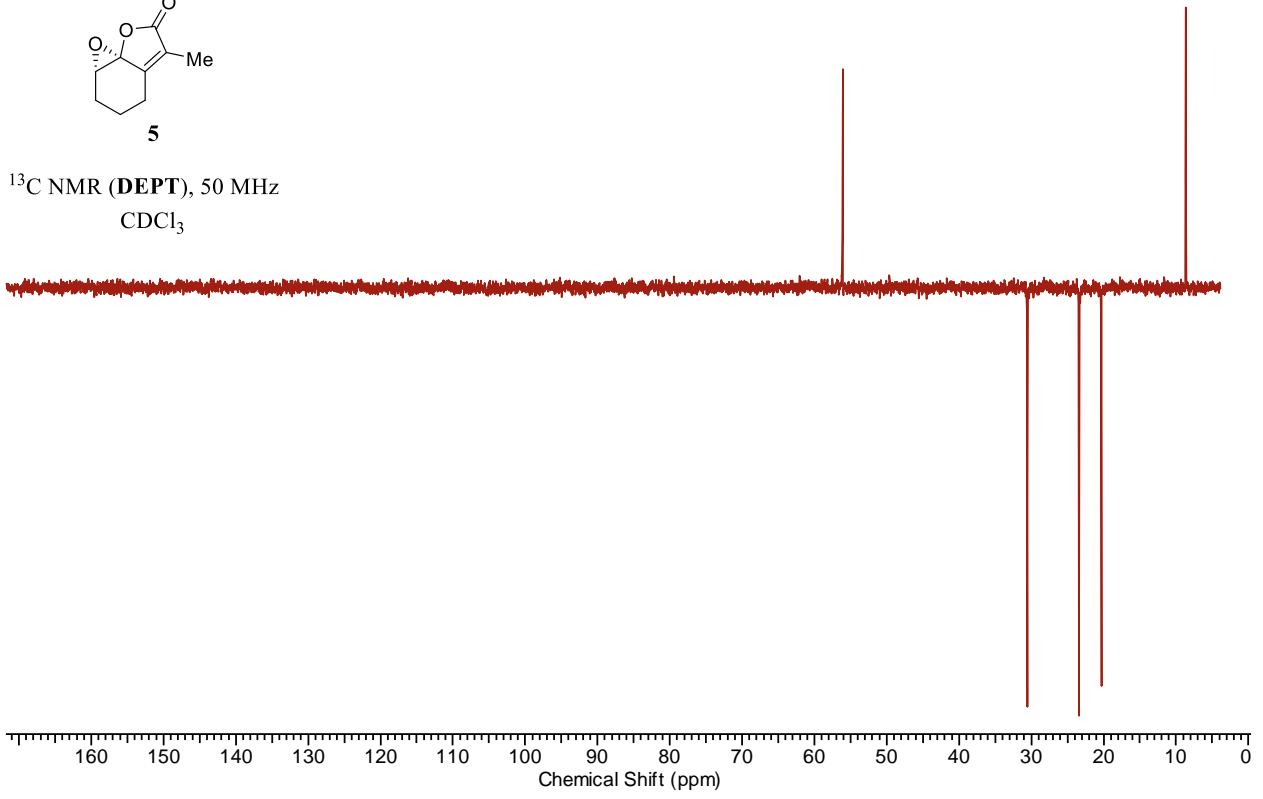


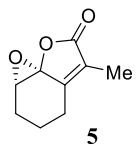
¹³C NMR, 50 MHz
CDCl₃



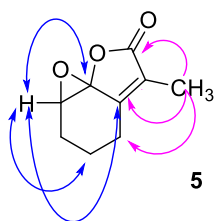
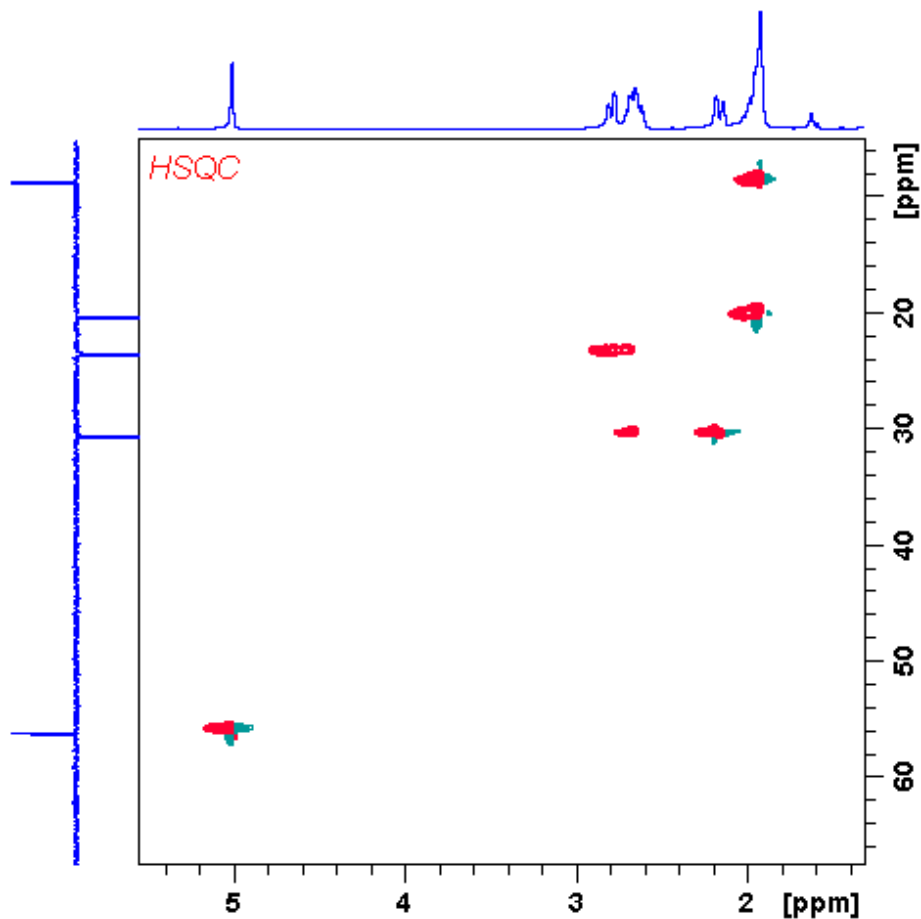


^{13}C NMR (DEPT), 50 MHz
 CDCl_3

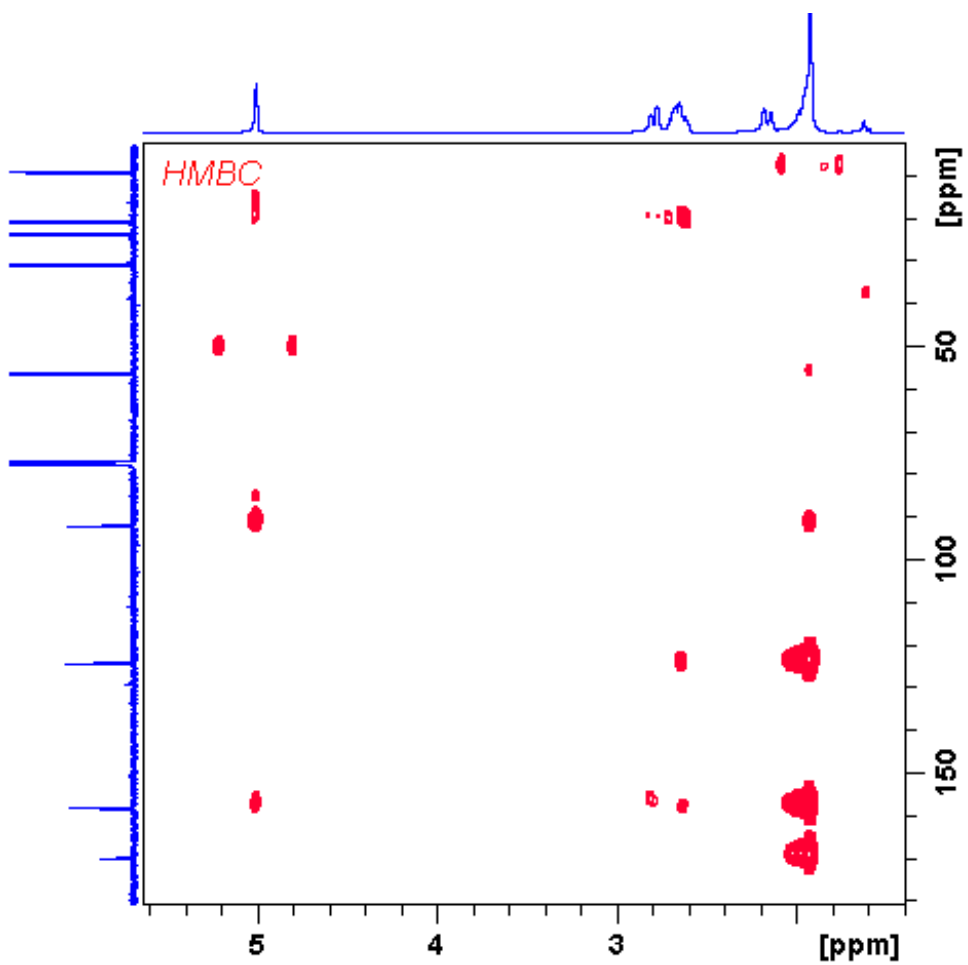




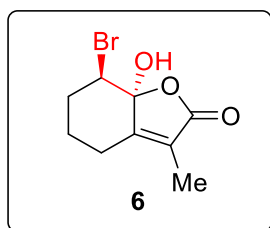
5
HSQC



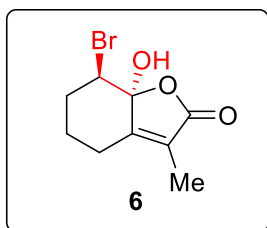
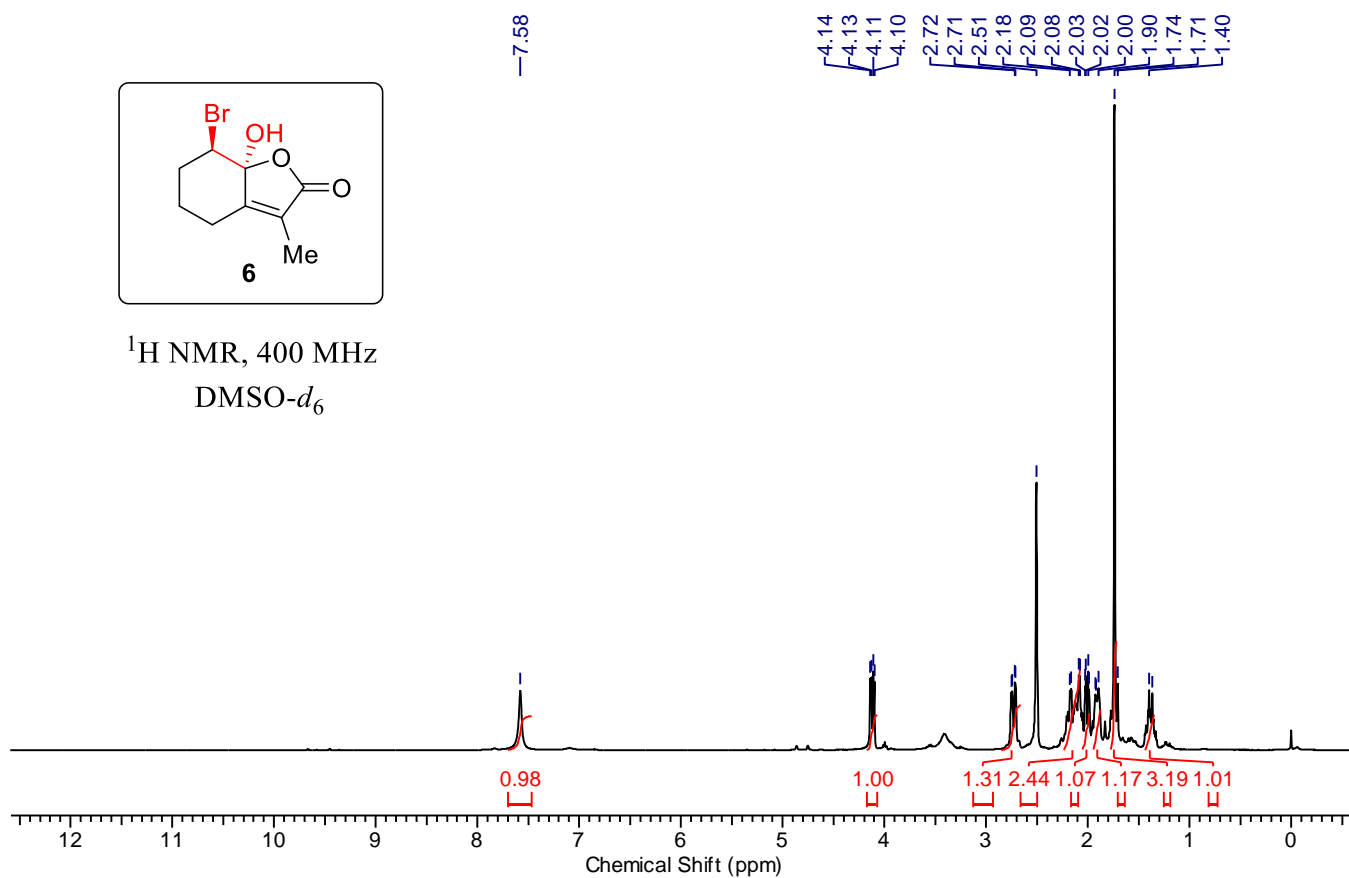
5
HMBC



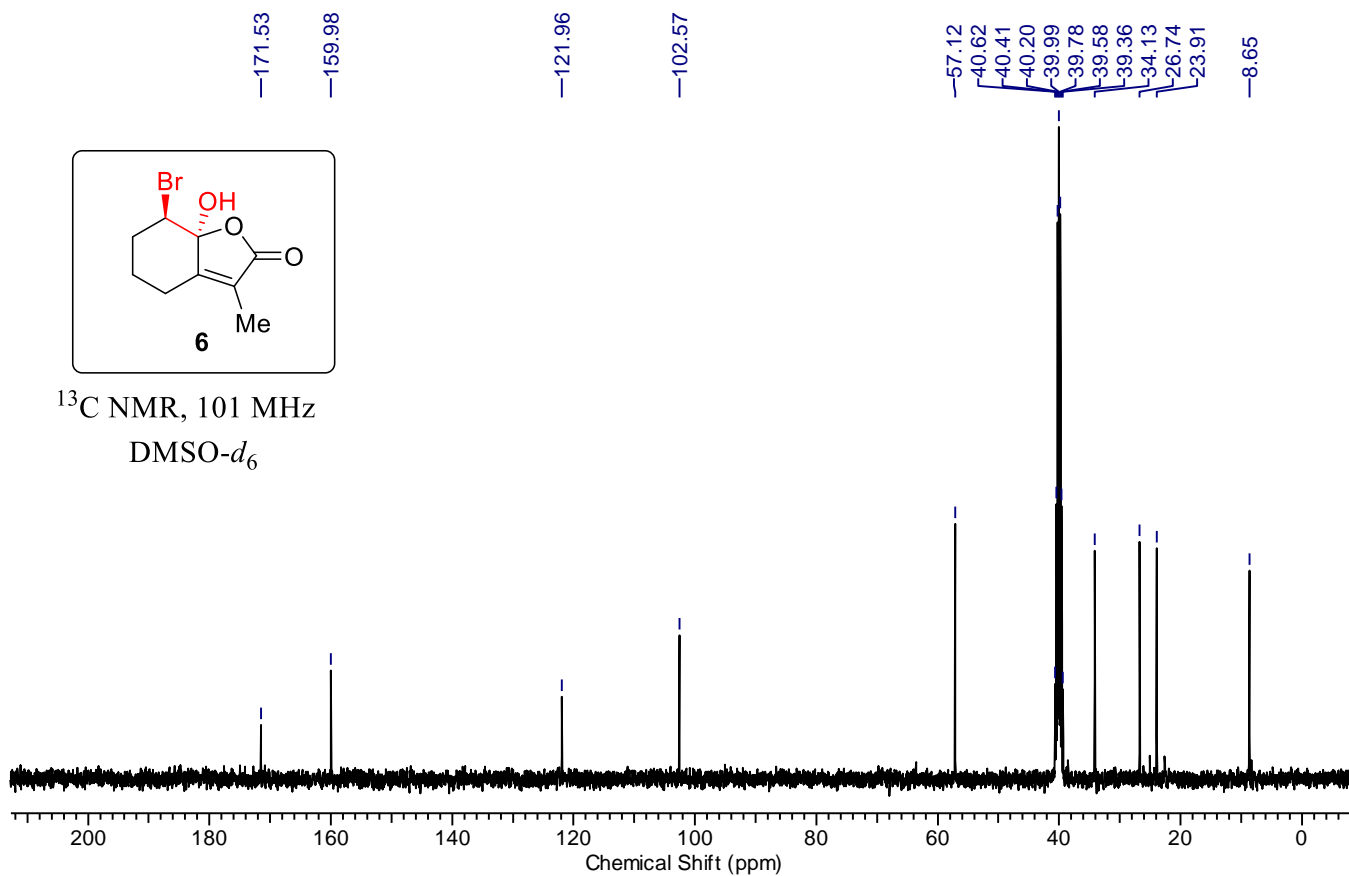
7-Bromo-7a-hydroxy-3-methyl-5,6,7,7a-tetrahydrobenzofuran-2(4H)-one (6):

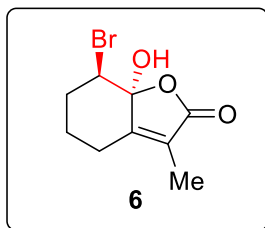


^1H NMR, 400 MHz
DMSO- d_6

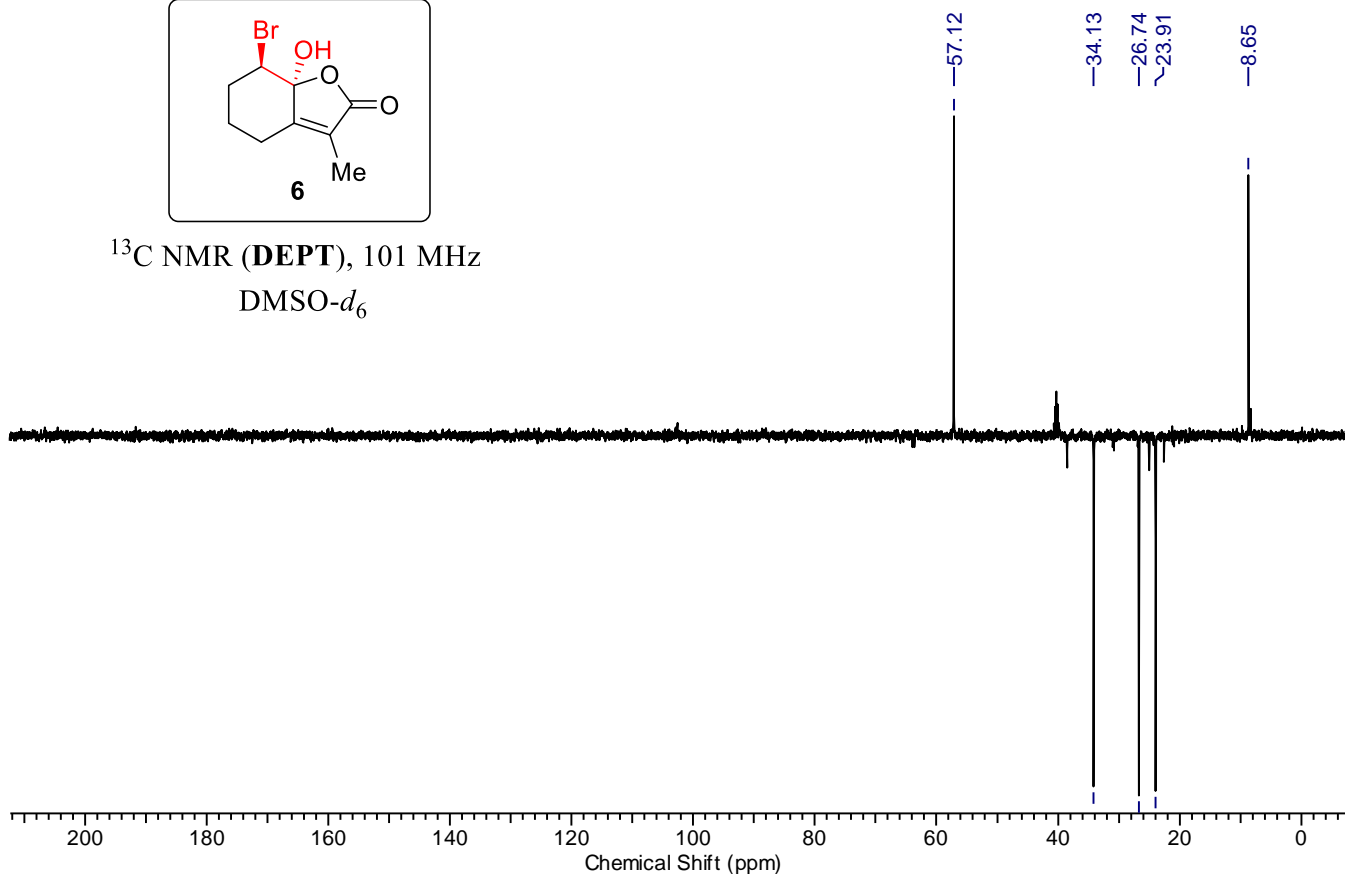


^{13}C NMR, 101 MHz
DMSO- d_6

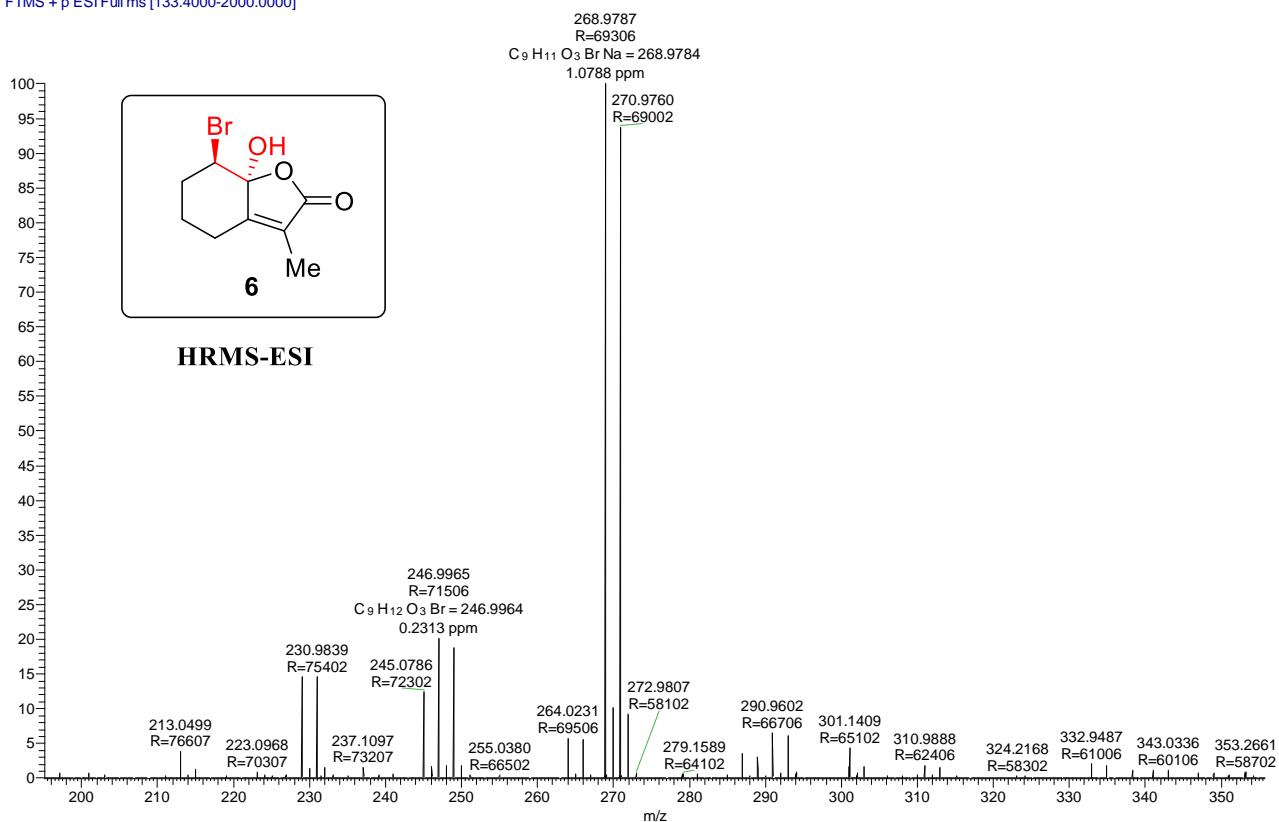


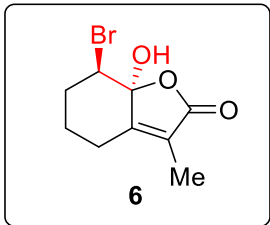


^{13}C NMR (DEPT), 101 MHz
DMSO- d_6

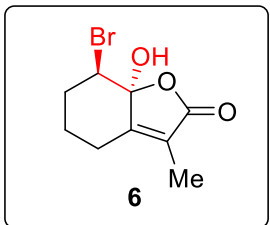
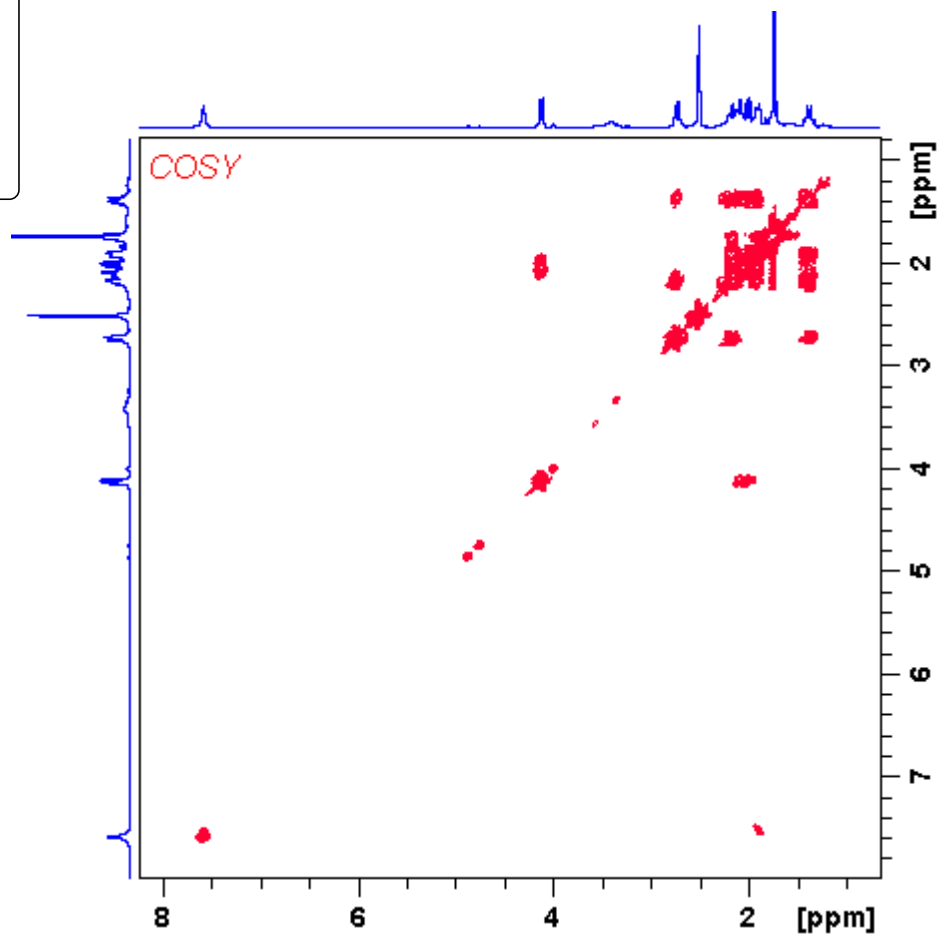


BB_2_15 #246 RT: 1.10 AV: 1 NL: 2.37E8
T: FTMS + p ESI Full ms [133.4000-2000.0000]

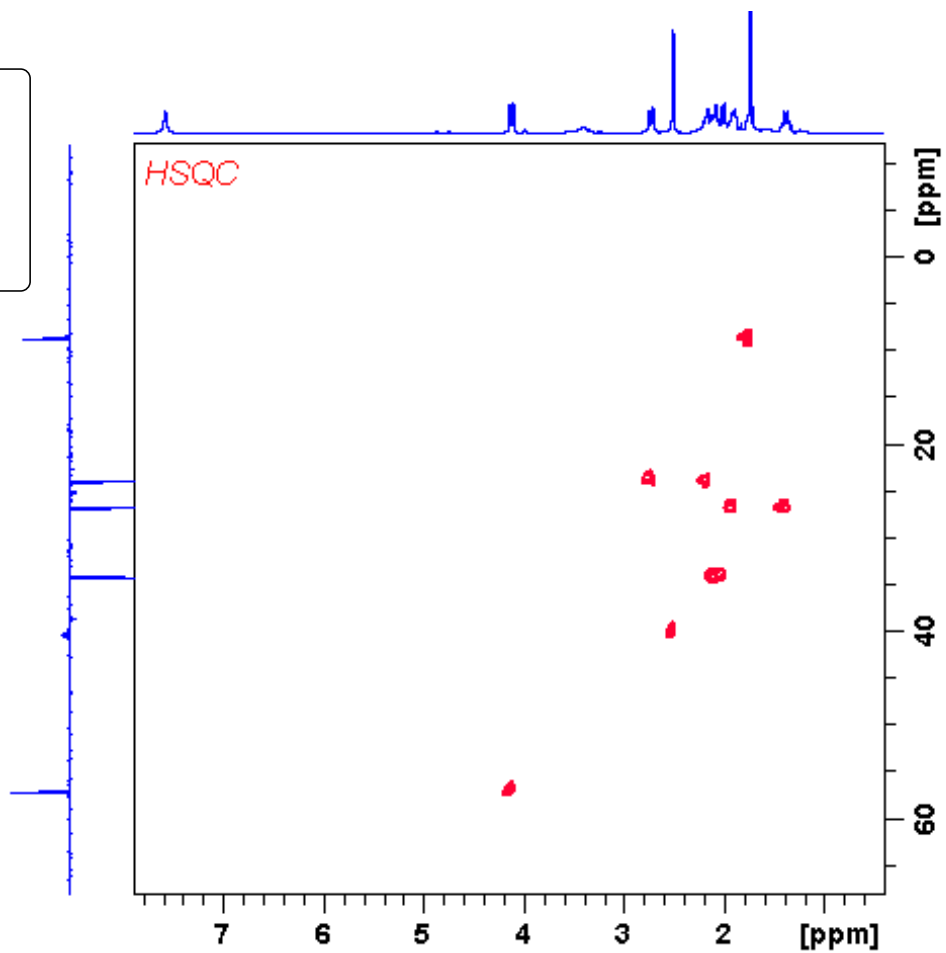


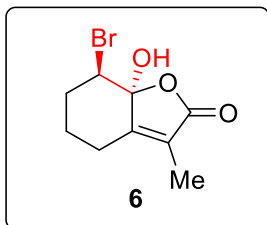


COSY

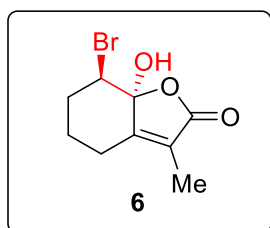
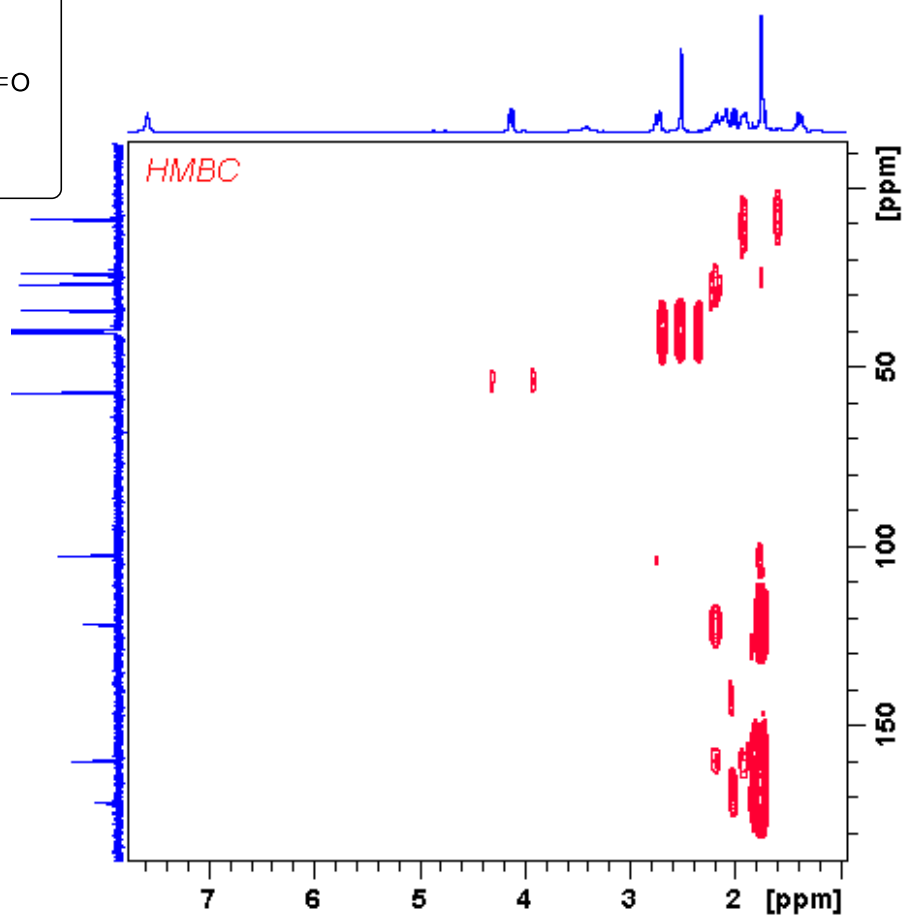


HSQC

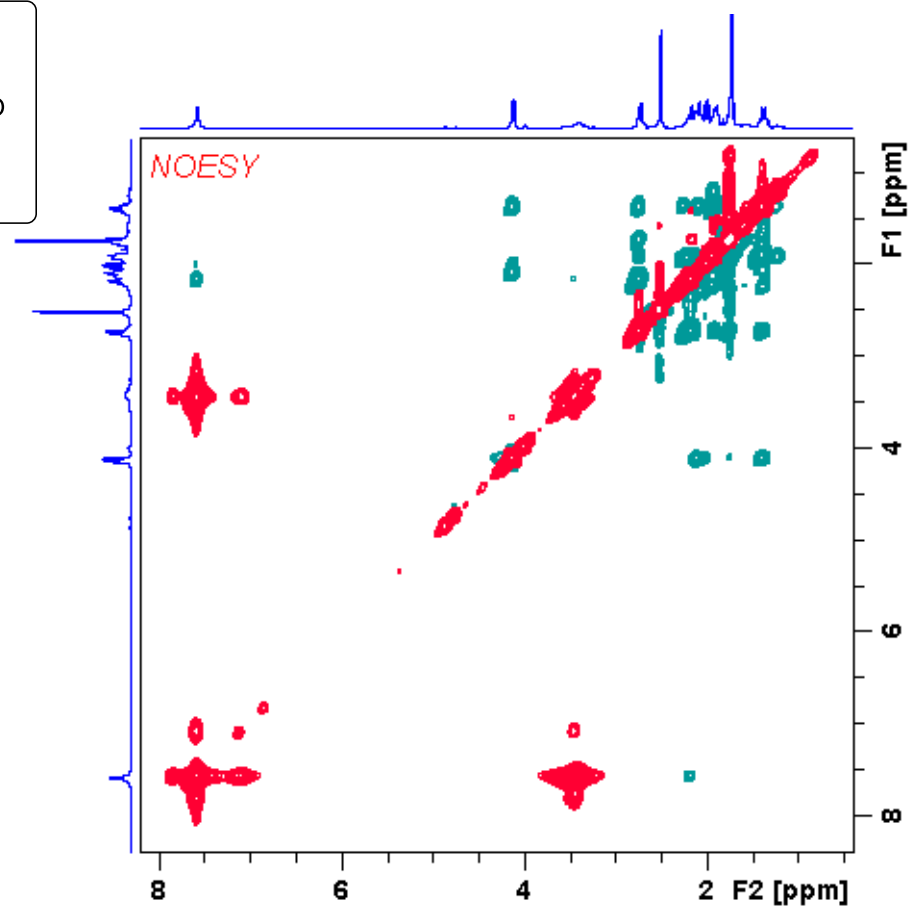




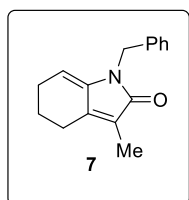
HMBC



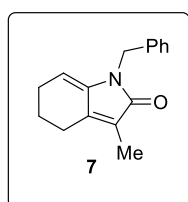
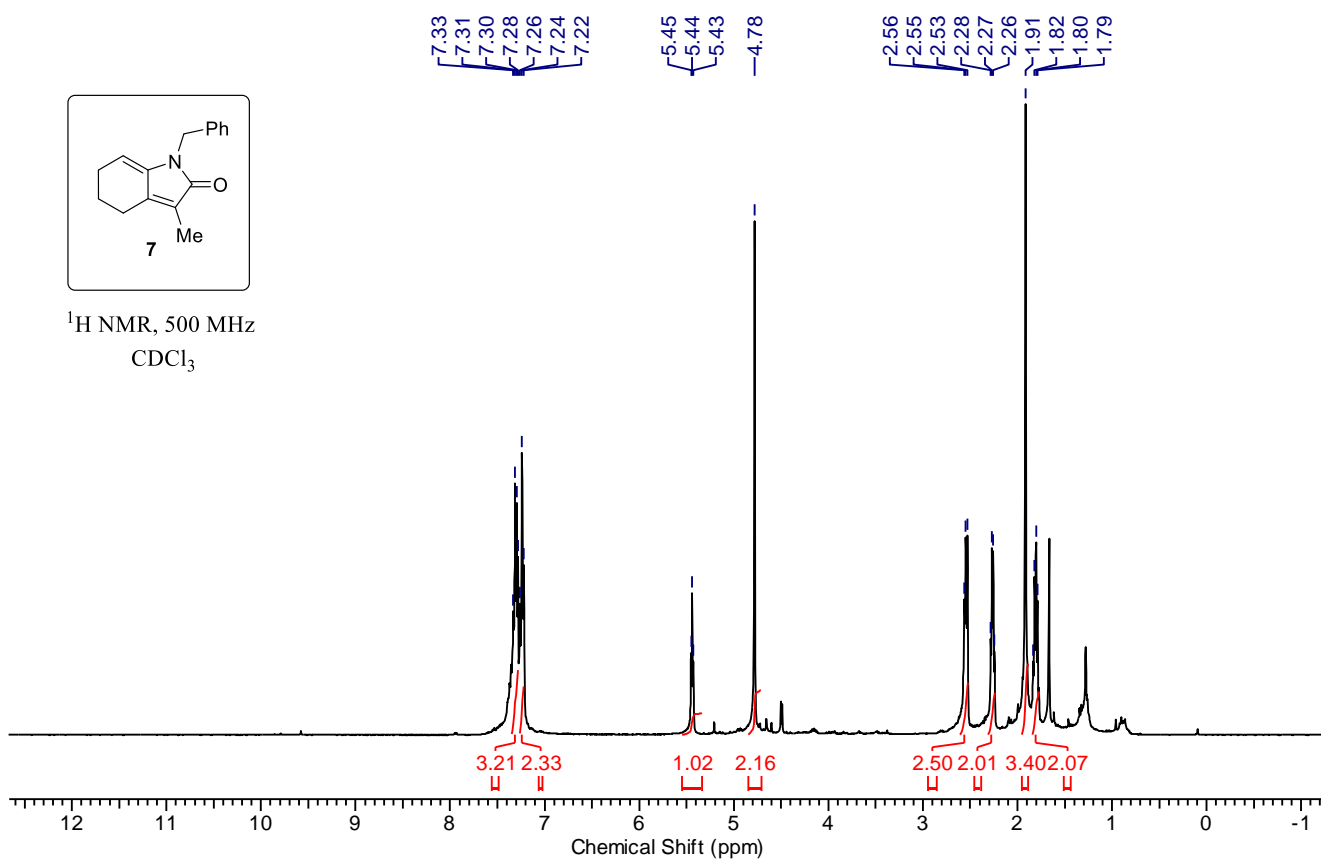
NOESY



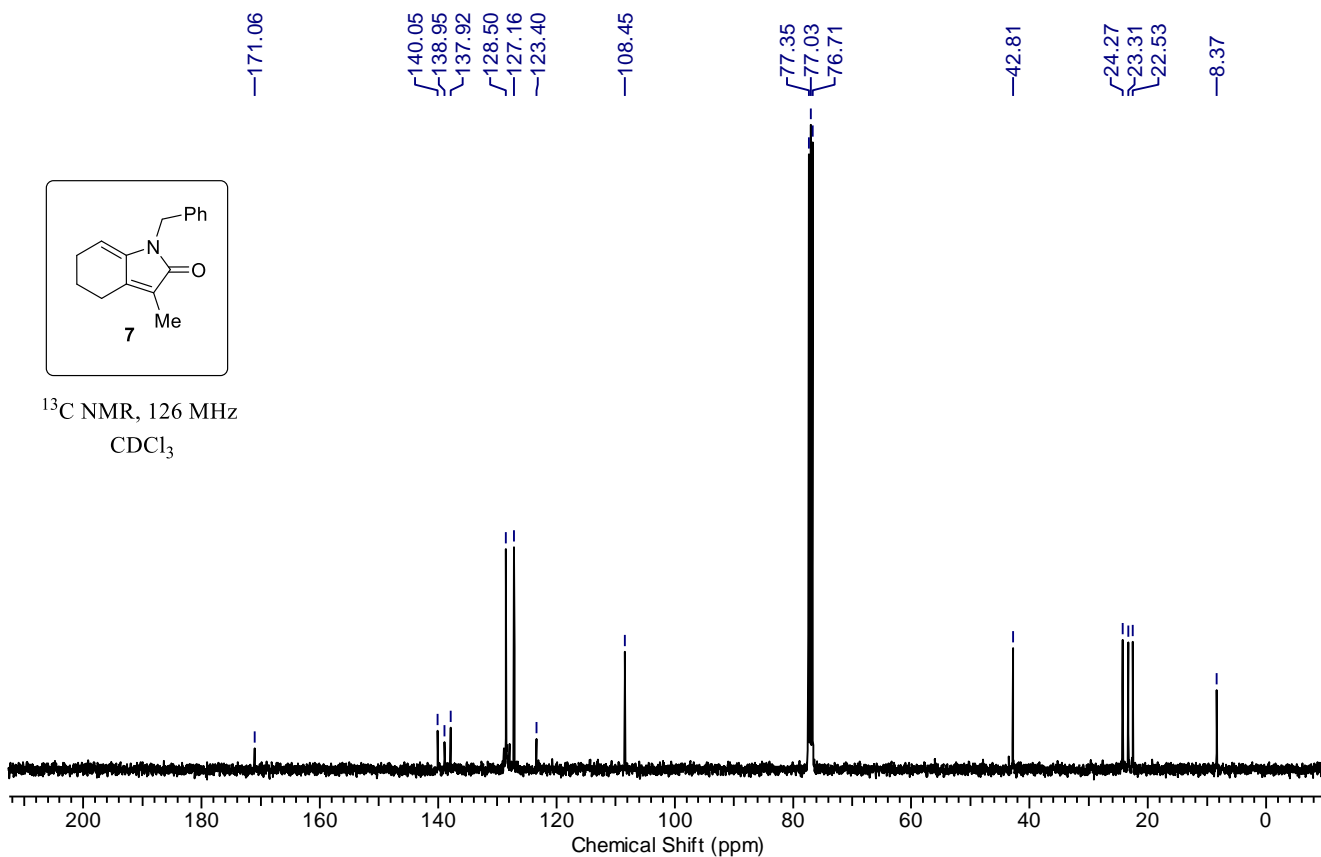
1-Benzyl-3-methyl-5,6-dihydro-1H-indol-2(4H)-one (7):



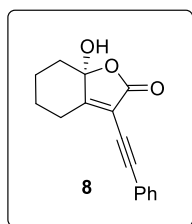
^1H NMR, 500 MHz
 CDCl_3



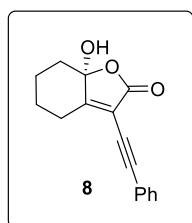
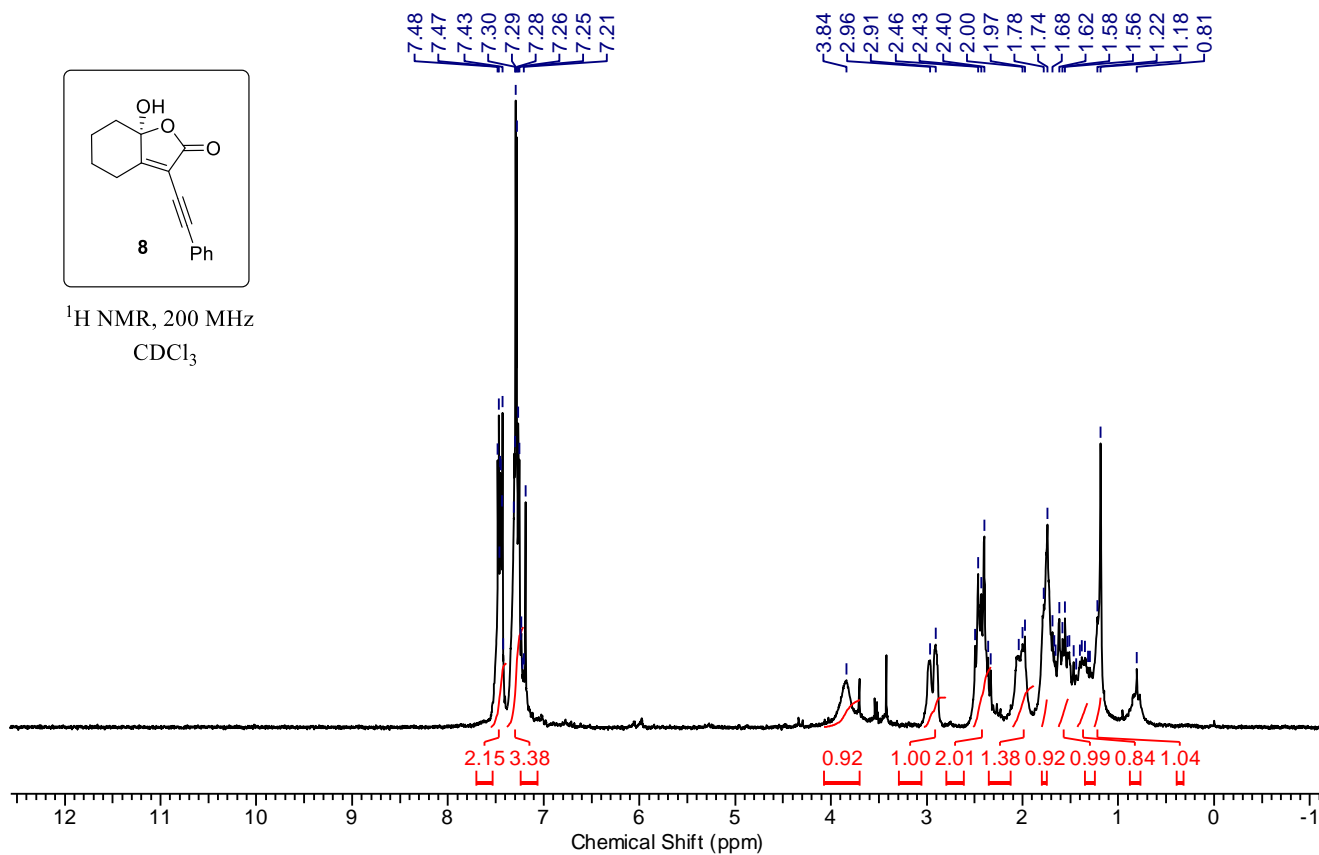
^{13}C NMR, 126 MHz
 CDCl_3



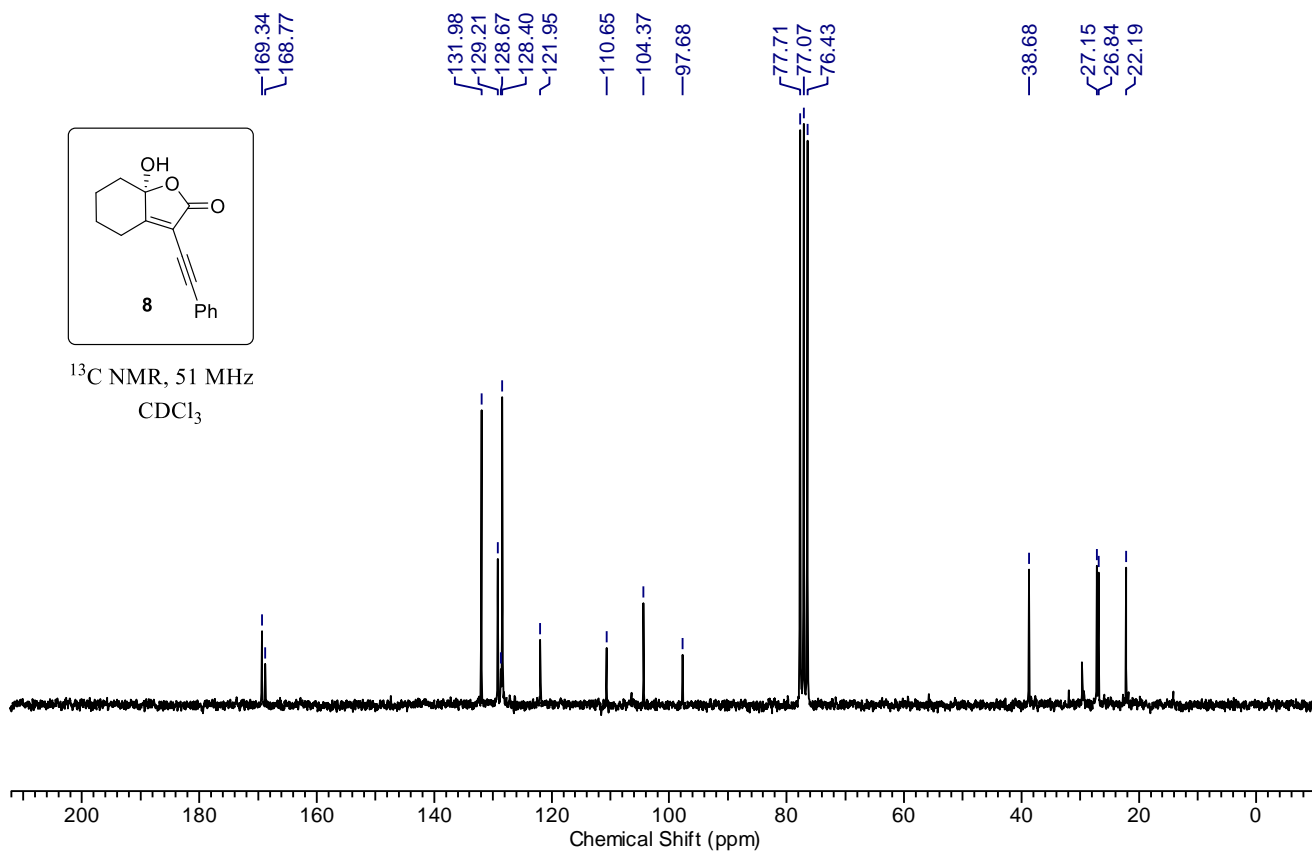
7a-Hydroxy-3-(phenylethynyl)-5,6,7,7a-tetrahydrobezofuran-2-(4H)-one (8):

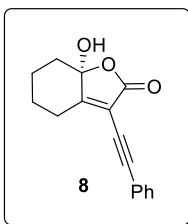


$^1\text{H NMR}$, 200 MHz
 CDCl_3

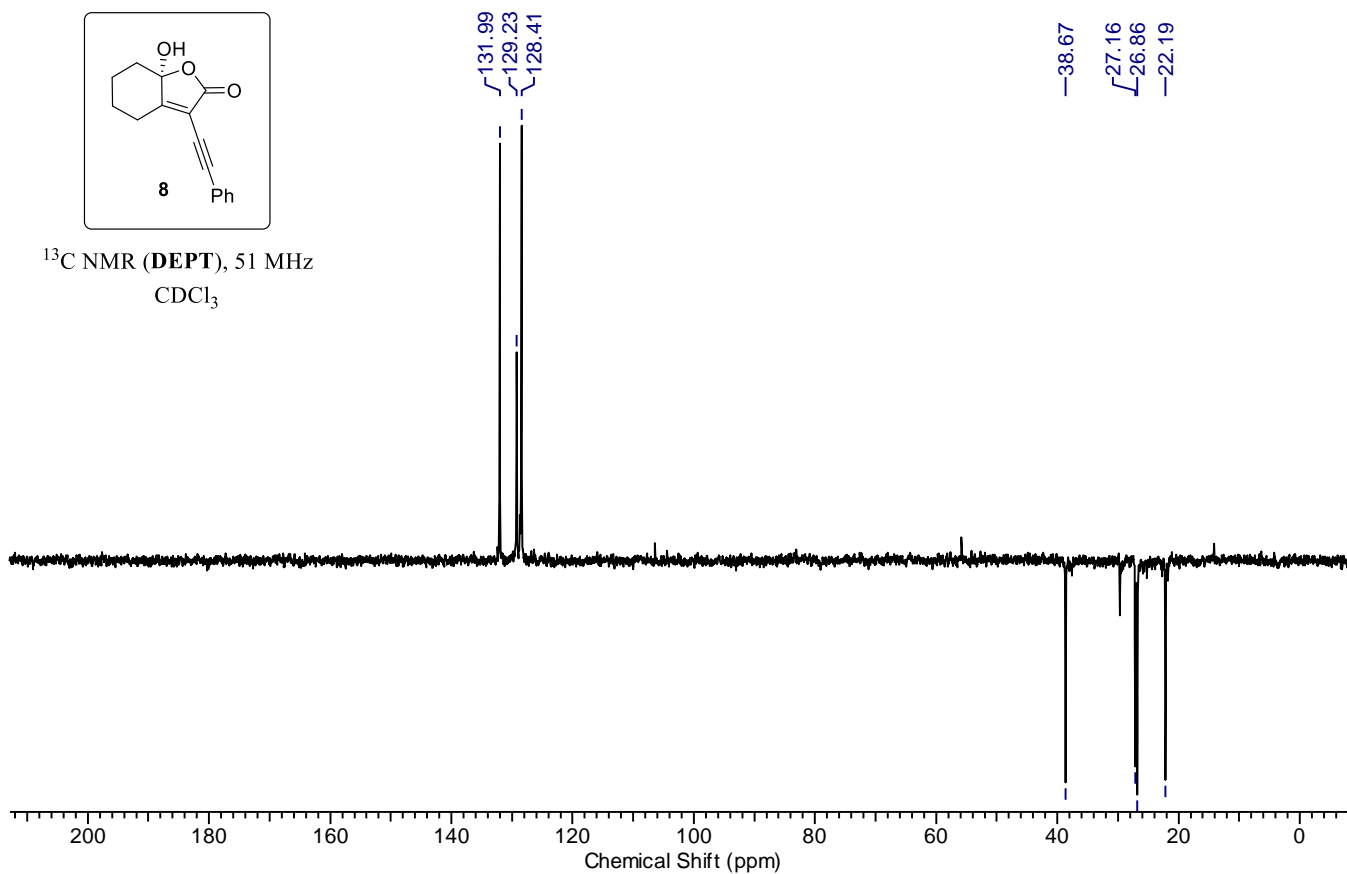


$^{13}\text{C NMR}$, 51 MHz
 CDCl_3





^{13}C NMR (DEPT), 51 MHz
 CDCl_3



MP-3 #267 RT: 1.20 AV: 1 NL: 1.89E8
 T: FTMS + p ESI Full ms [133.4000-2000.0000]

