SUPPORTING INFORMATION

Synthesis of 3,3-Disubstituted Thietane Dioxides

Peerawat Saejong,[a] Jaining Zhong,[a] Juan J. Rojas,[a] Andrew J. P. White,[a] Chulho Choi,[b] and James A. Bull[a]*

[a] Department of Chemistry, Imperial College London, Molecular Sciences Research Hub, White City Campus, Wood Lane W12 0BZ, UK
[b] Pfizer Worldwide Research, Development and Medical, Eastern Point Rd., Groton, CT 06340, USA.

*E-mail: j.bull@imperial.ac.uk

Preparation of single crystals

2a: Single crystals of **2a** were grown by dissolving the compound in a solvent mixture of CH_2Cl_2 and hexane (6:4) at 40 °C. The warm mixture (2.0 mL) was added to **2a** (3.1 mg) in a 3 mL vial, which was then capped and left at room temperature until crystals formed.
3aa: For the growth of single crystals of **3aa**, acetone was used to dissolve the compound in a 3 mL vial. The vial was then loosely capped and placed inside a 10 mL vial containing 1.0 mL of heptane. The larger vial was sealed and stored at –20 °C until crystal formation was observed.
3ac and **5aa:** Single crystals of **3ac** and **5aa** were grown slowly in $CDCl_3$ at room temperature.

Crystal Data, Data Collection and Refinement Parameters

Table S1. Crystal Data, Data Collection and Refinement Parameters for the structures of **2a**, **3aa**, **3ac** and **5aa**.

data	2a	3aa	3ac	5aa
formula	$C_{10}H_{12}O_4S$	$C_{17}H_{18}O_4S$	$C_{18}H_{20}O_4S$	$C_{17}H_{18}O_3S_2$
formula weight	228.26	318.37	332.40	334.43
colour, habit	colourless needles	colourless blocks	colourless tablets	colourless tablets
temperature / K	173	173	173	173
crystal system	monoclinic	orthorhombic	monoclinic	monoclinic
space group	$P2_1/c$ (no. 14)	$P2_12_12_1$ (no. 19)	$P2_1/c$ (no. 14)	$P2_1/c$ (no. 14)
***a* / Å**	5.6198(3)	9.1214(2)	7.0019(2)	13.0110(3)
***b* / Å**	6.9237(3)	11.1350(3)	11.1321(3)	5.89527(15)
***c* / Å**	25.4955(12)	15.0959(4)	20.8963(6)	21.4203(6)
α / deg	90	90	90	90
β / deg	96.029(5)	90	95.061(3)	91.614(3)
γ / deg	90	90	90	90
***V* / Å^3**	986.54(8)	1533.24(6)	1622.43(8)	1642.35(8)
Z	4	4	4	4
***D*$_c$ / g cm^{-3}**	1.537	1.379	1.361	1.353
radiation used	Cu-Kα	Mo-Kα	Cu-Kα	Cu-Kα
μ / mm^{-1}	2.876	0.227	1.927	3.018
no. of unique reflns				
measured (*R*$_{int}$)	1938 (0.0296)	3464 (0.0397)	3130 (0.0358)	3271 (0.0395)
obs, $\|F_o\| > 4\sigma(\|F_o\|)$	1618	3161	2360	2673
completeness (%) [a]	99.9	99.9	98.7	99.8
no. of variables	142	206	216	202
***R*$_1$(obs), *wR*$_2$(all)** [b]	0.0363, 0.1035	0.0335, 0.0800	0.0423, 0.1181	0.0372, 0.1027
CCDC code	2368330	2368331	2368332	2368333

[a] Completeness to 0.84 Å resolution. [b] $R_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$; $wR_2 = \{\Sigma[w(F_o^2 - F_c^2)^2] / \Sigma[w(F_o^2)^2]\}^{1/2}$; $w^{-1} = \sigma^2(F_o^2) + (aP)^2 + bP$.

Table S1 provides a summary of the crystallographic data for the structures of **2a**, **3aa**, **3ac** and **5aa**. Data were collected using Agilent Xcalibur PX Ultra A (**2a**, **3ac** and **5aa**) and Agilent Xcalibur 3 E (**3aa**) diffractometers, and the structures were solved and refined using the OLEX2,[1] SHELXTL[2] and SHELX-2013[3] program systems. The absolute structure of **3aa** was determined by use of the Flack parameter [$x = 0.00(3)$]. CCDC 2368330 to 2368333.

X-Ray crystallography

The O15–H hydrogen atom in the structure of **2a** was located from a Δ*F* map and refined freely subject to an O–H distance constraint of 0.90 Å. Whilst the structure of **2a** can be modelled using a half volume unit cell based on halving the *c* axis length, this results in a significantly disordered model in a chiral space group with an indeterminate Flack parameter [*x* = 0.25(11)]. The version presented here using the longer *c* axis, however, has no disorder in a centrosymmetric space group and is thus much preferred. The O22–H hydrogen atom in the structure of **3aa** was located from a Δ*F* map and refined freely subject to an O–H distance constraint of 0.90 Å. The absolute structure of **3aa** was determined by use of the Flack parameter [*x* = 0.00(3)]. The O22–H hydrogen atom in the structure of **3ac** was located from a Δ*F* map and refined freely subject to an O–H distance constraint of 0.90 Å.

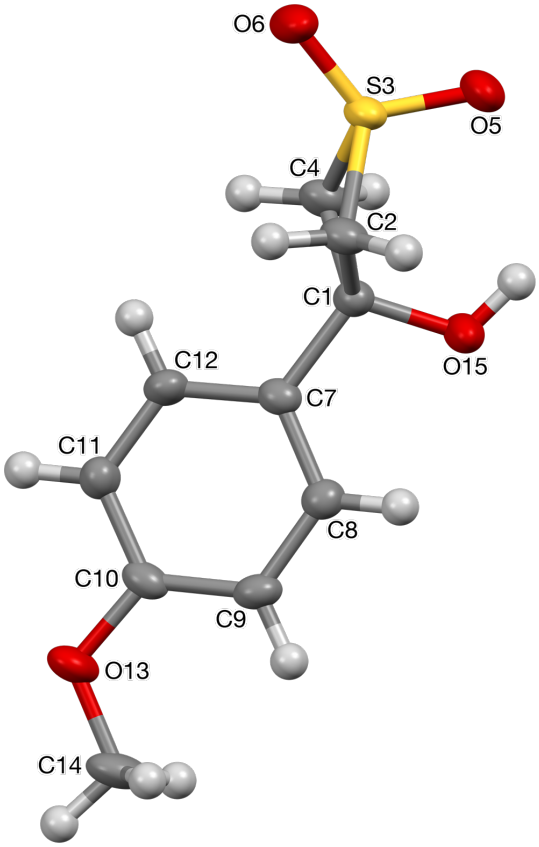


Fig. S1 The crystal structure of **2a** (65% probability ellipsoids).

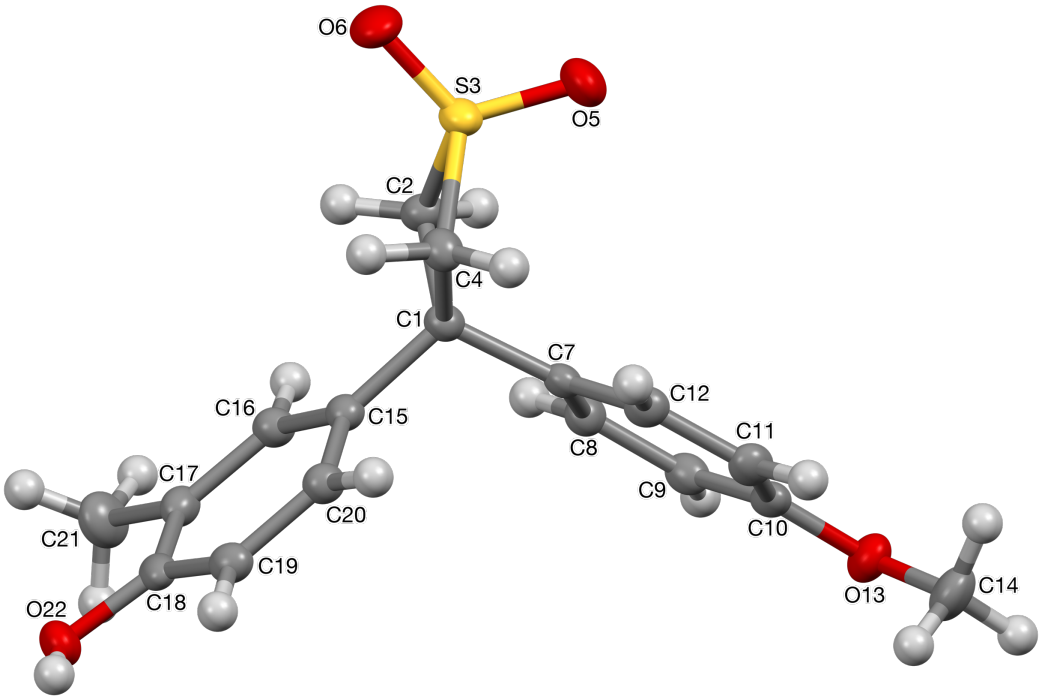


Fig. S2 The crystal structure of **3aa** (50% probability ellipsoids).

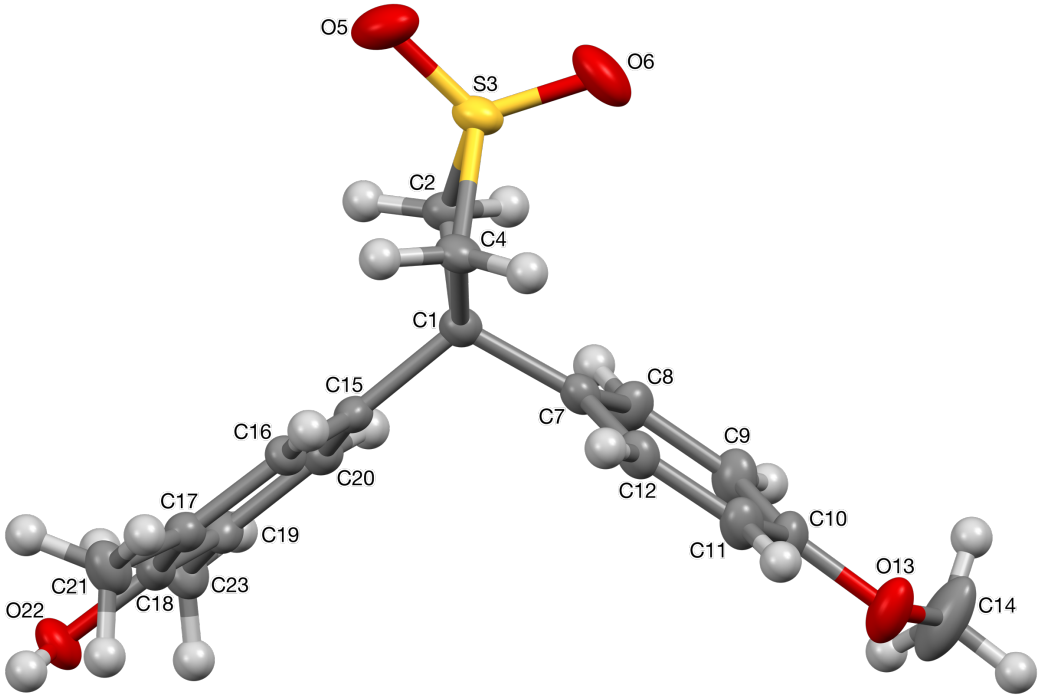


Fig. S3 The crystal structure of **3ac** (50% probability ellipsoids).

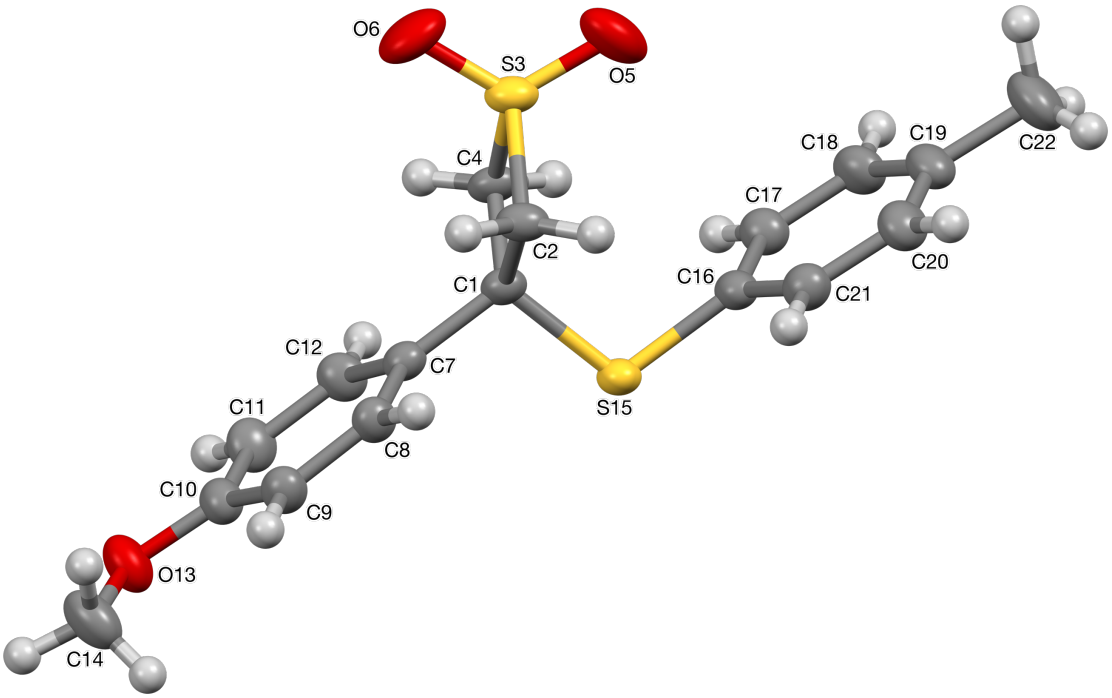
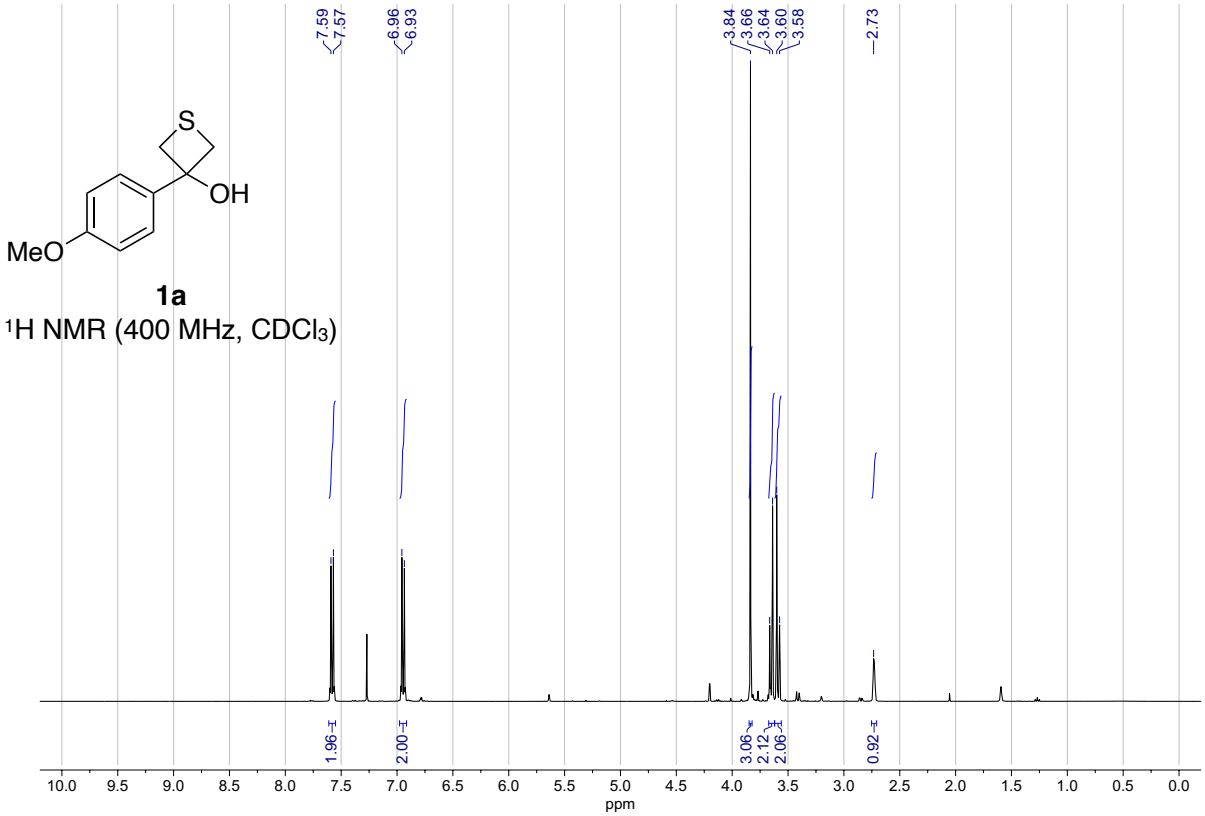


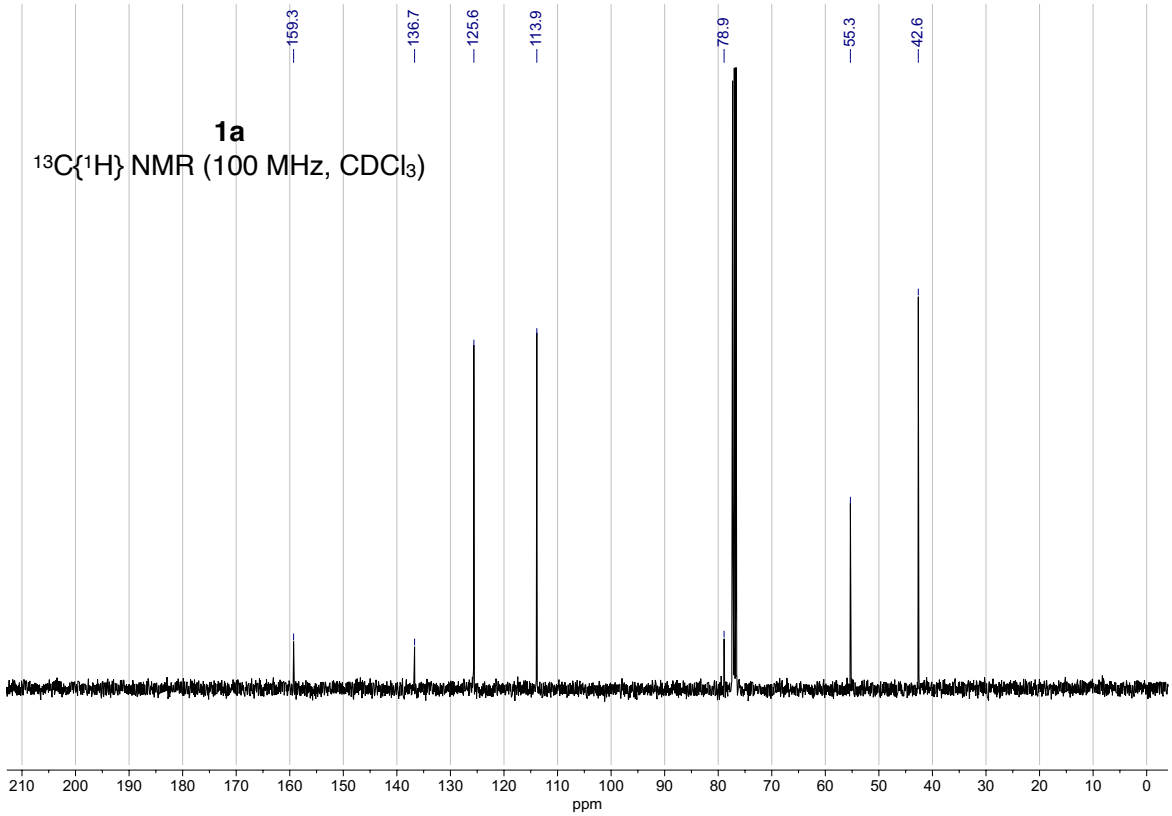
Fig. S4 The crystal structure of **5aa** (50% probability ellipsoids).

^{1}H and ^{13}C NMR Spectra of Selected Compounds



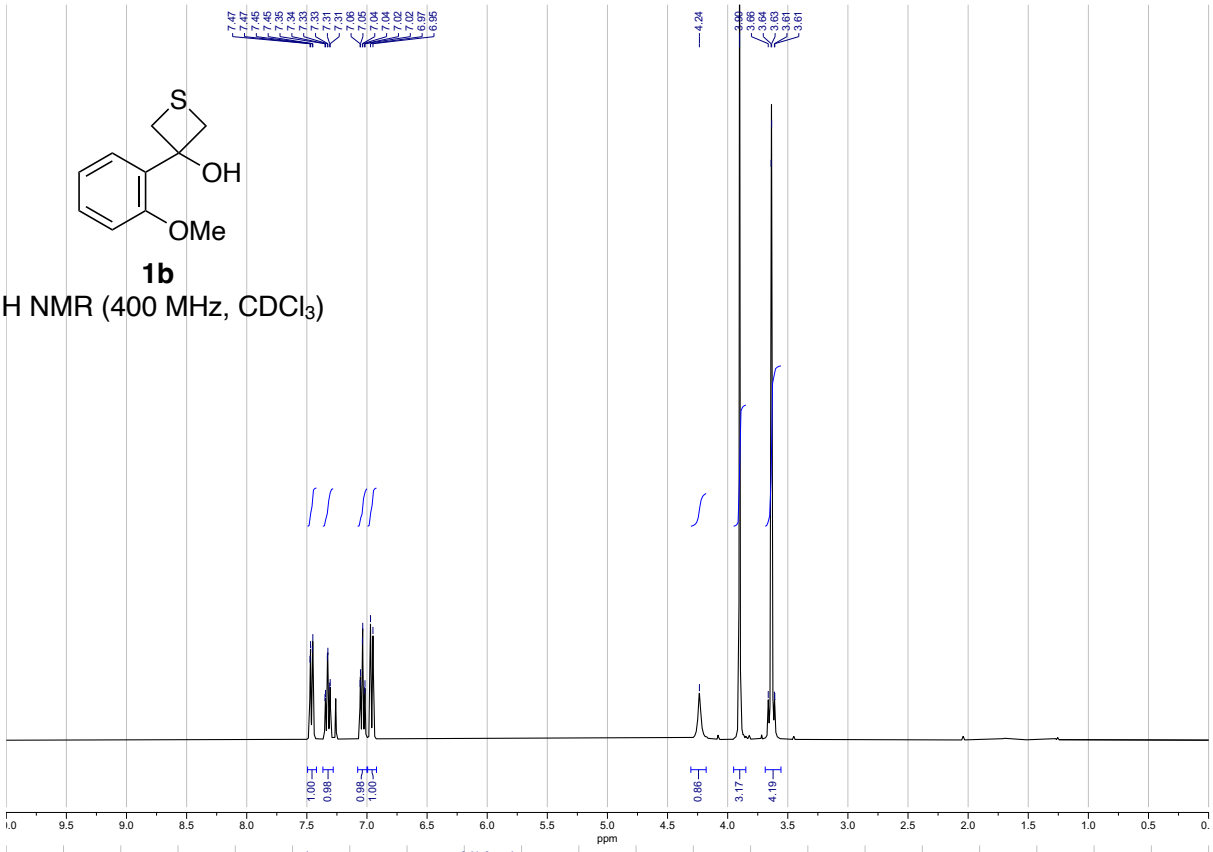
1a

^{1}H NMR (400 MHz, $CDCl_3$)



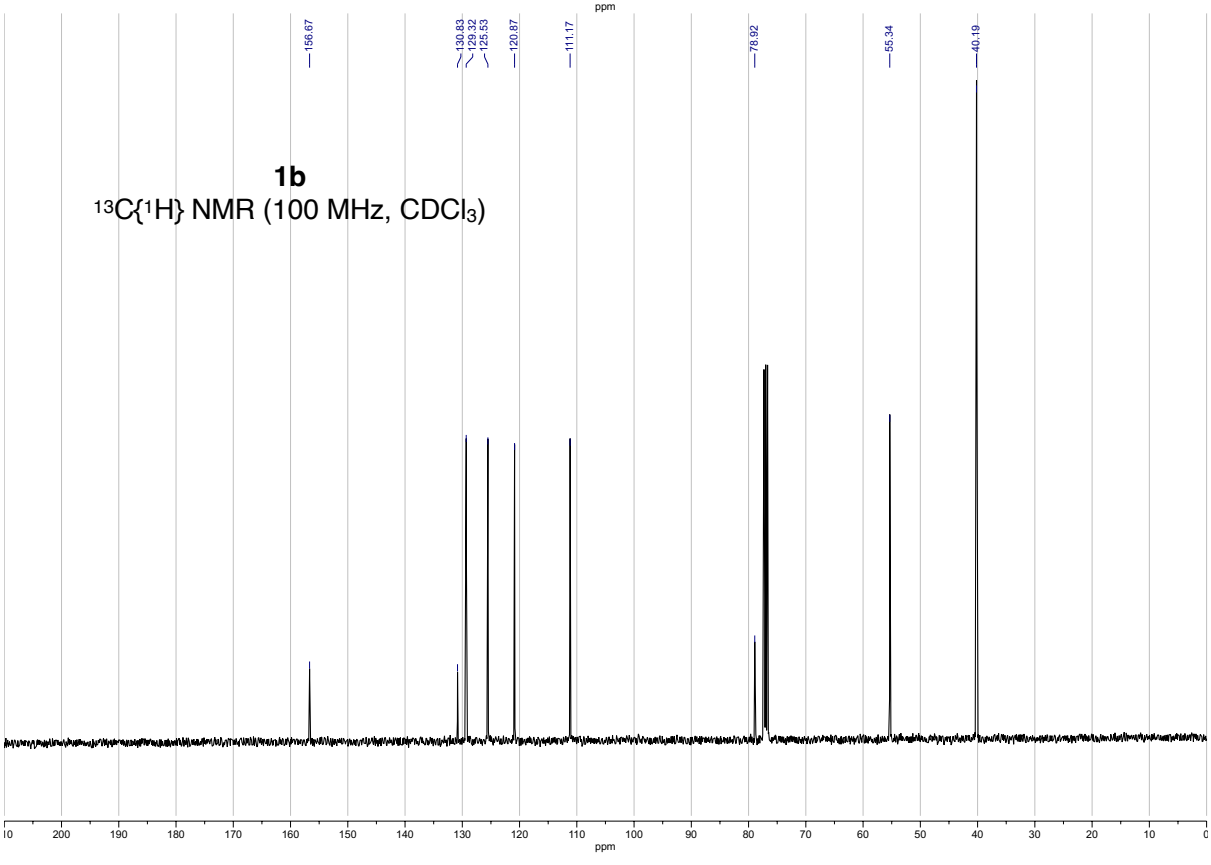
1a

$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$)



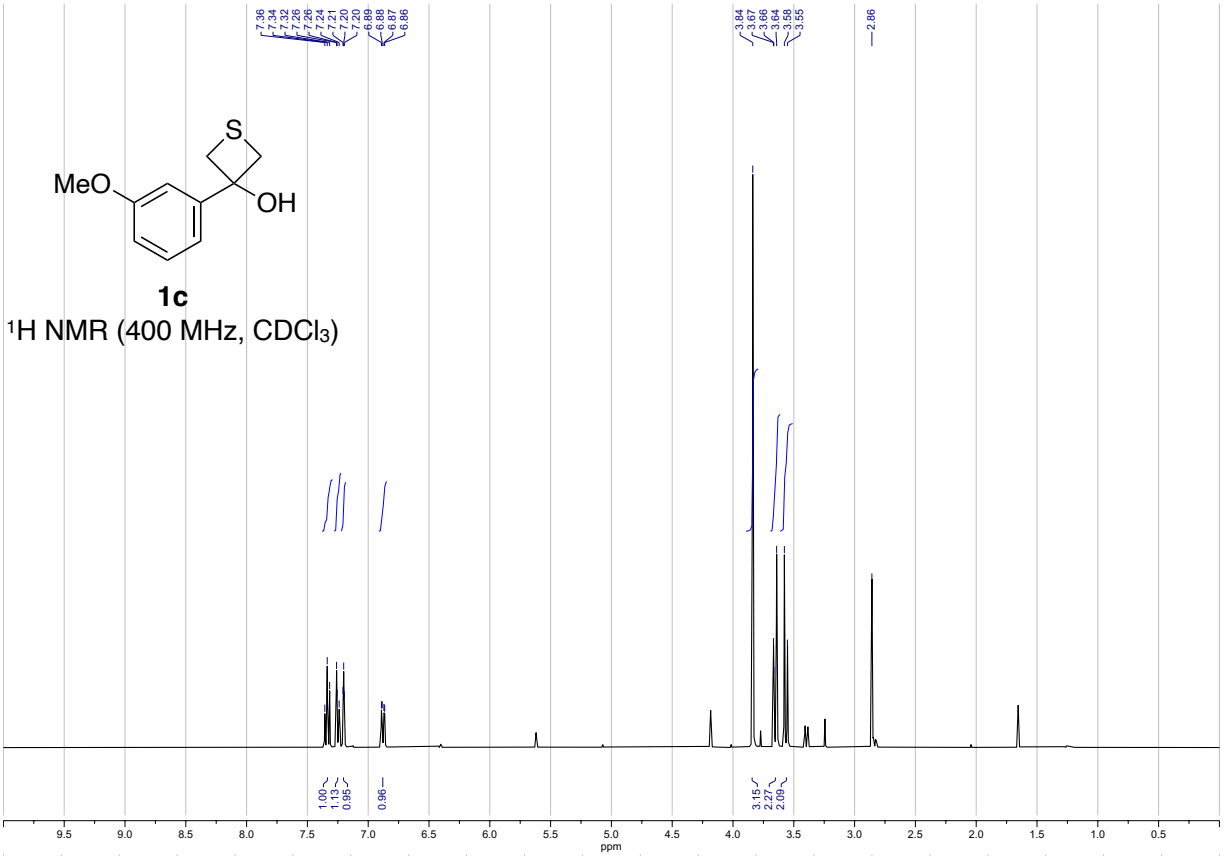
1b

^{1}H NMR (400 MHz, $CDCl_3$)



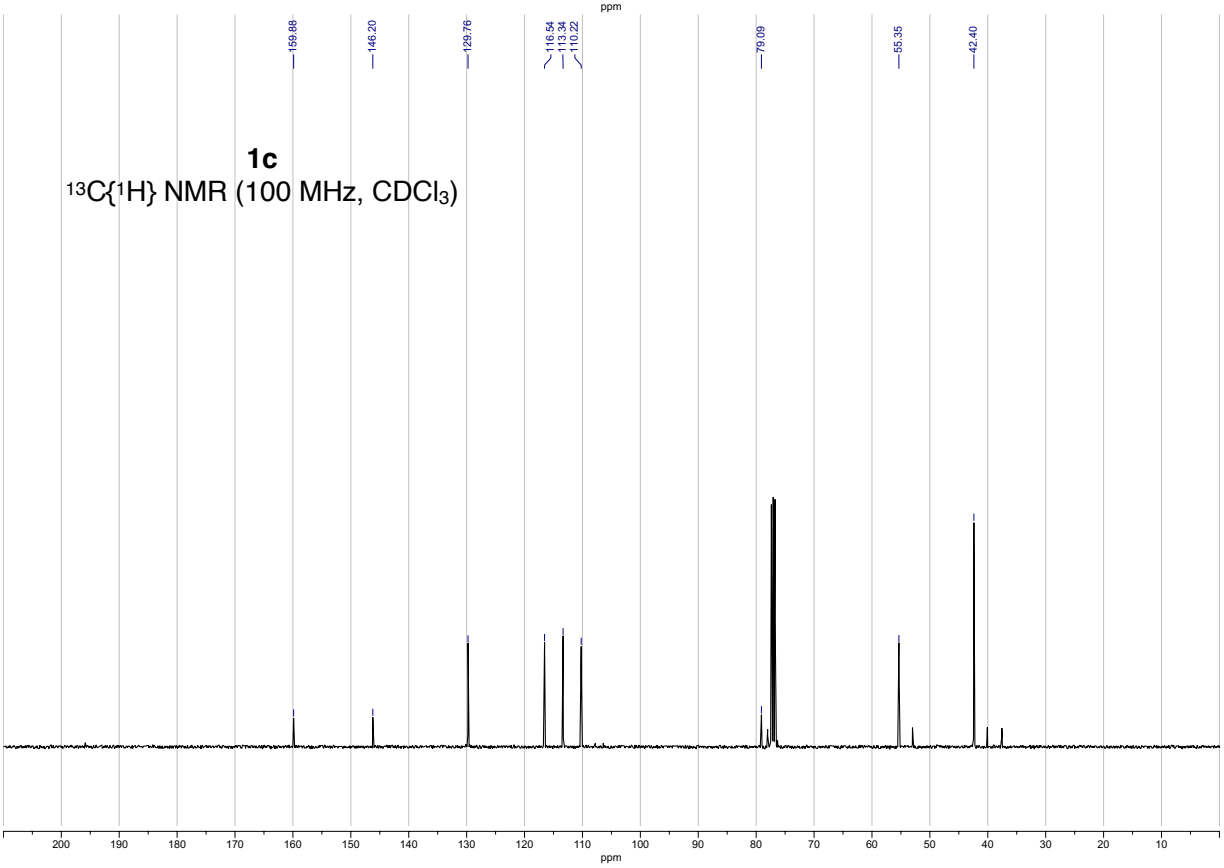
1b

$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$)



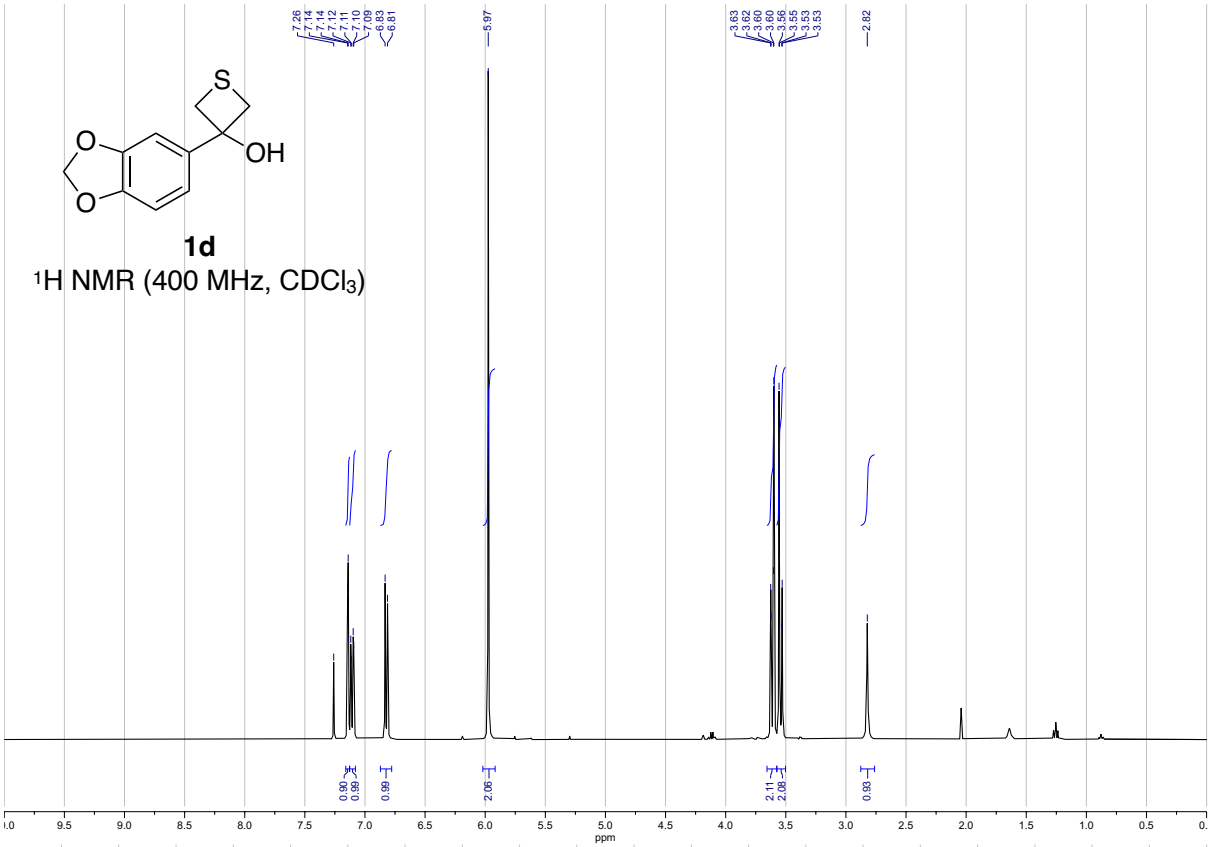
1c

^{1}H NMR (400 MHz, $CDCl_3$)



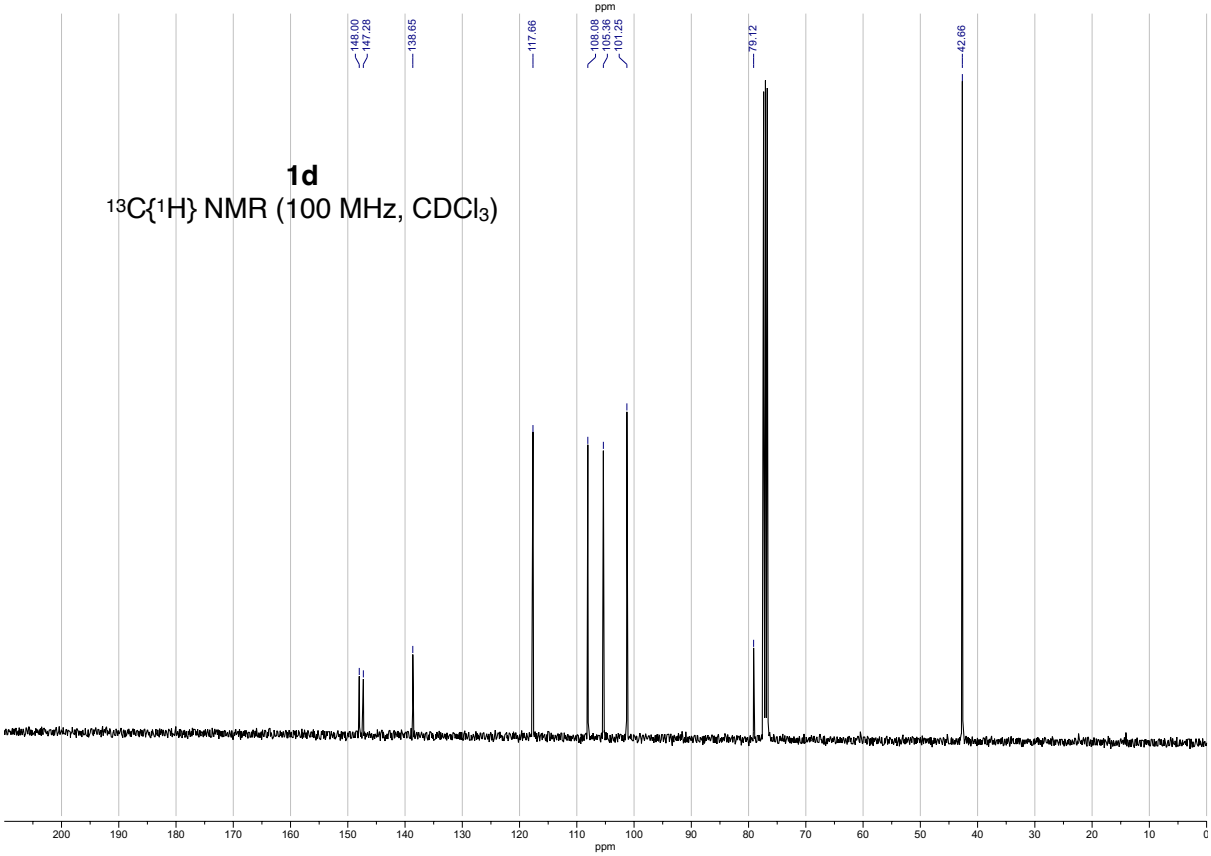
1c

$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$)



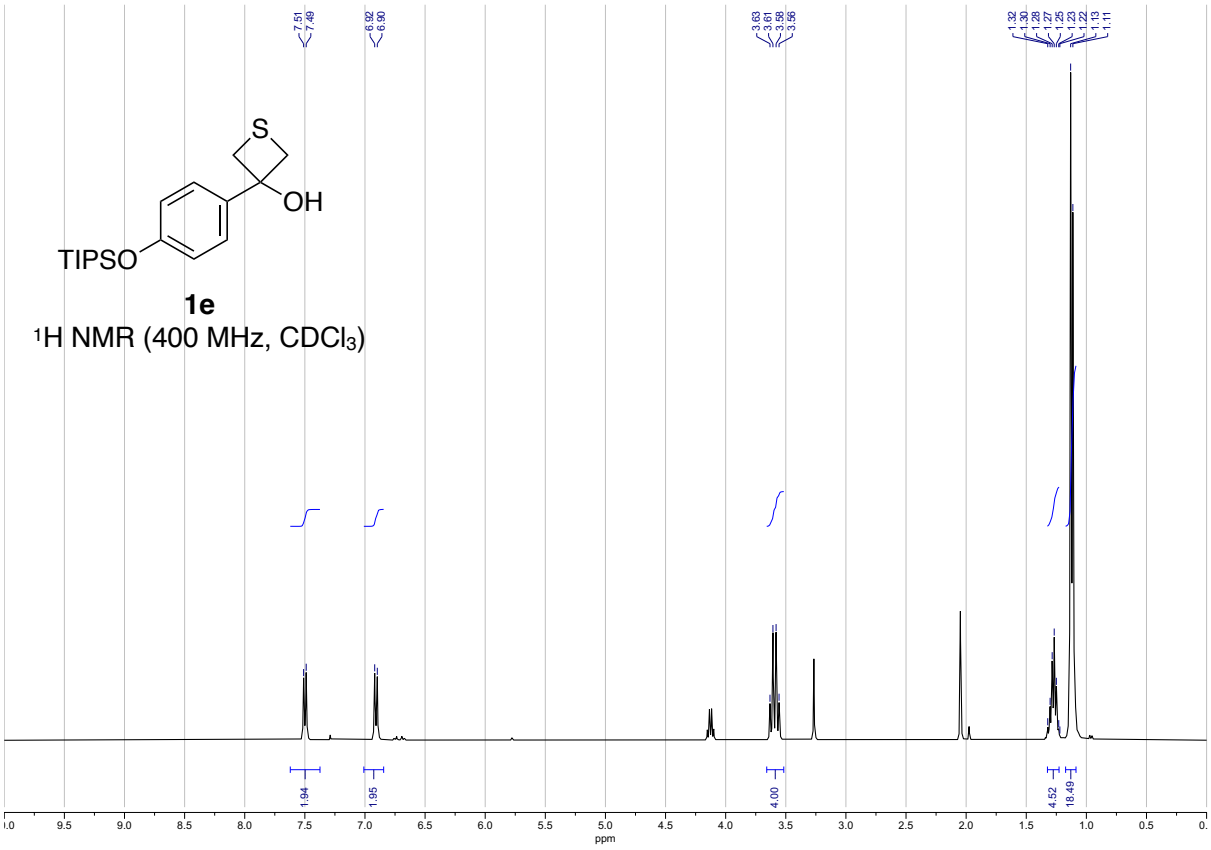
1d

^{1}H NMR (400 MHz, $CDCl_3$)



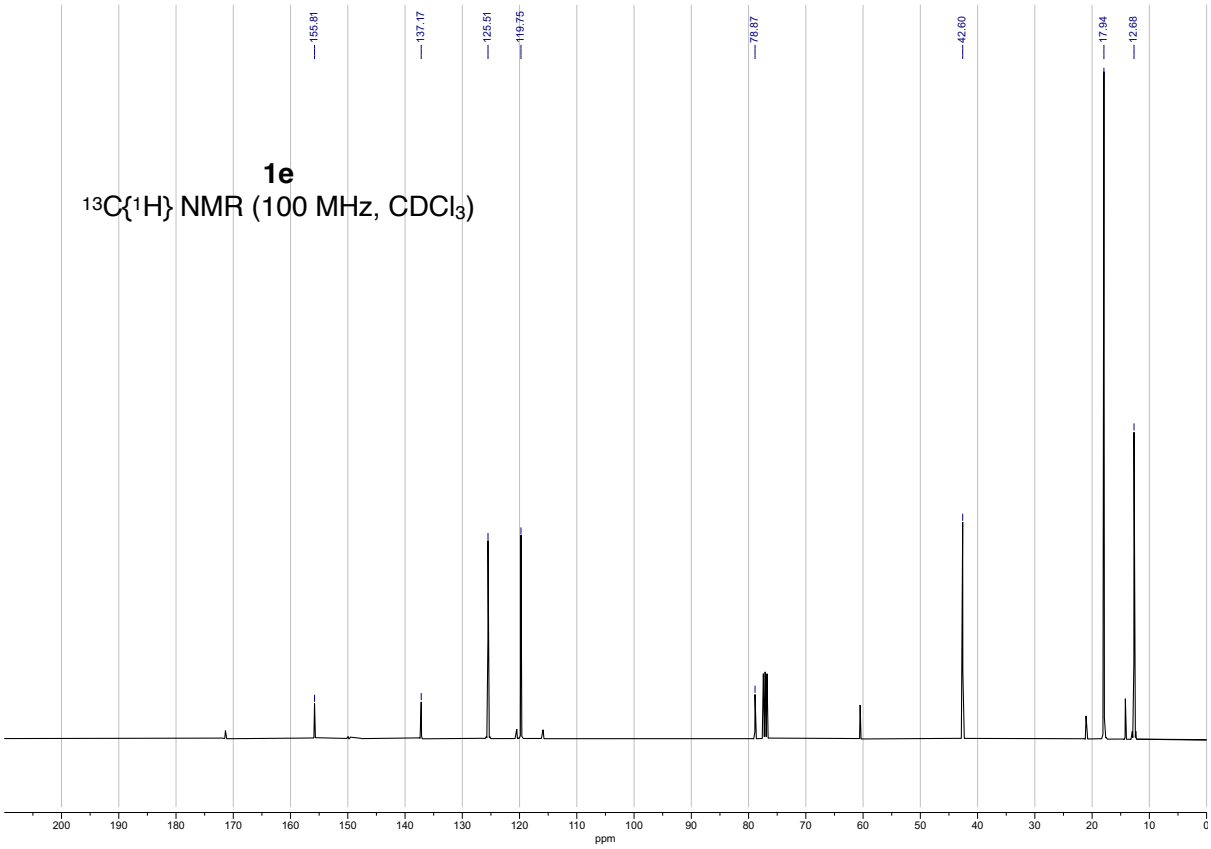
1d

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)



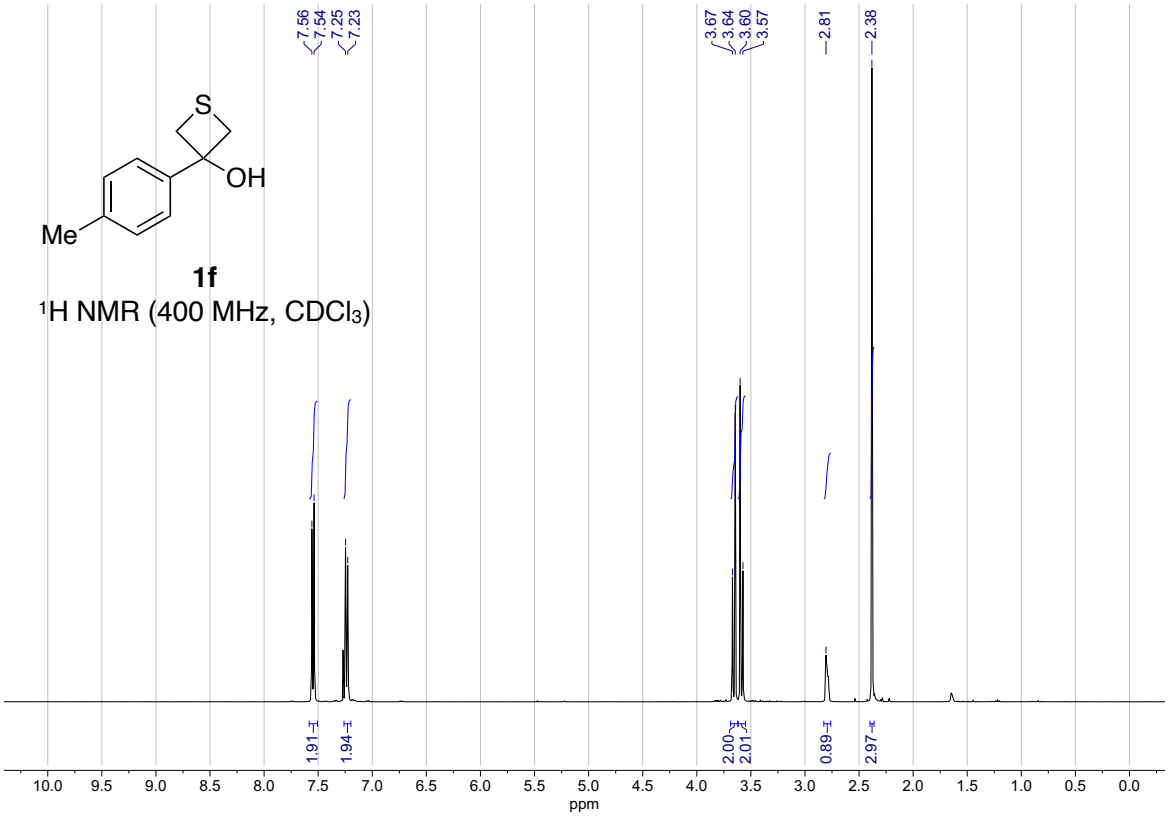
1e

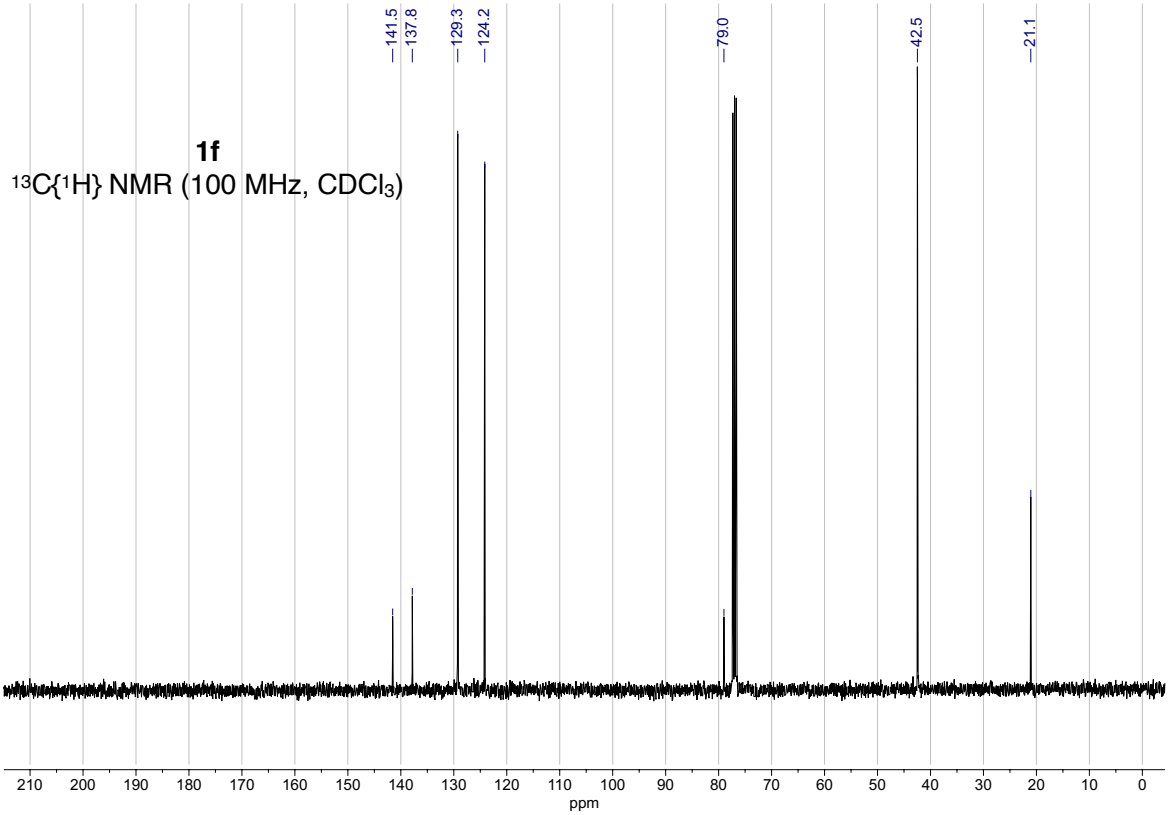
^{1}H NMR (400 MHz, $CDCl_3$)

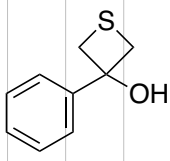


1e

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)


7.56
7.54
7.25
7.23
3.67
3.64
3.60
3.57
2.81
2.38
S
OH
Me
1f
^{1}H NMR (400 MHz, CDCl$_3$)
1.91
1.94
2.00
2.01
0.89
2.97
ppm


141.5
137.8
129.3
124.2
79.0
42.5
21.1
1f
^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$)
ppm

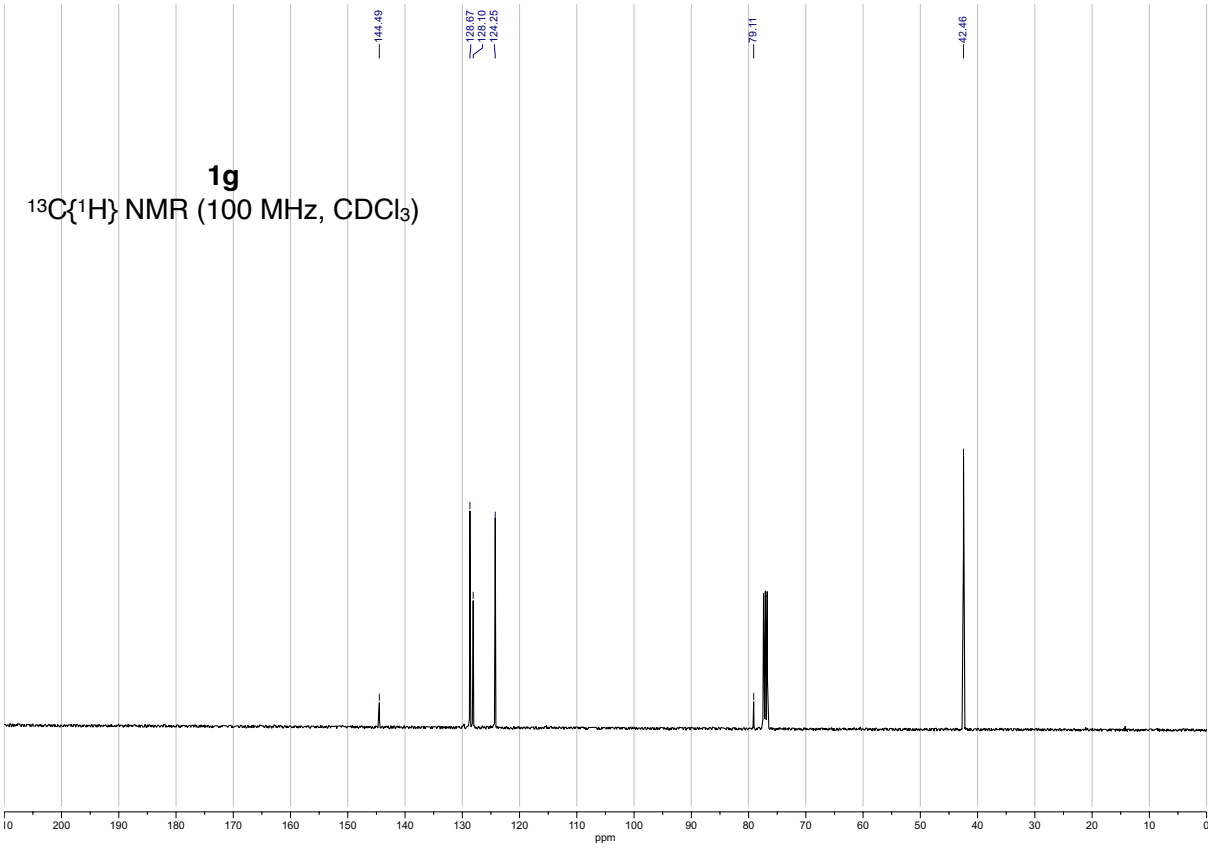


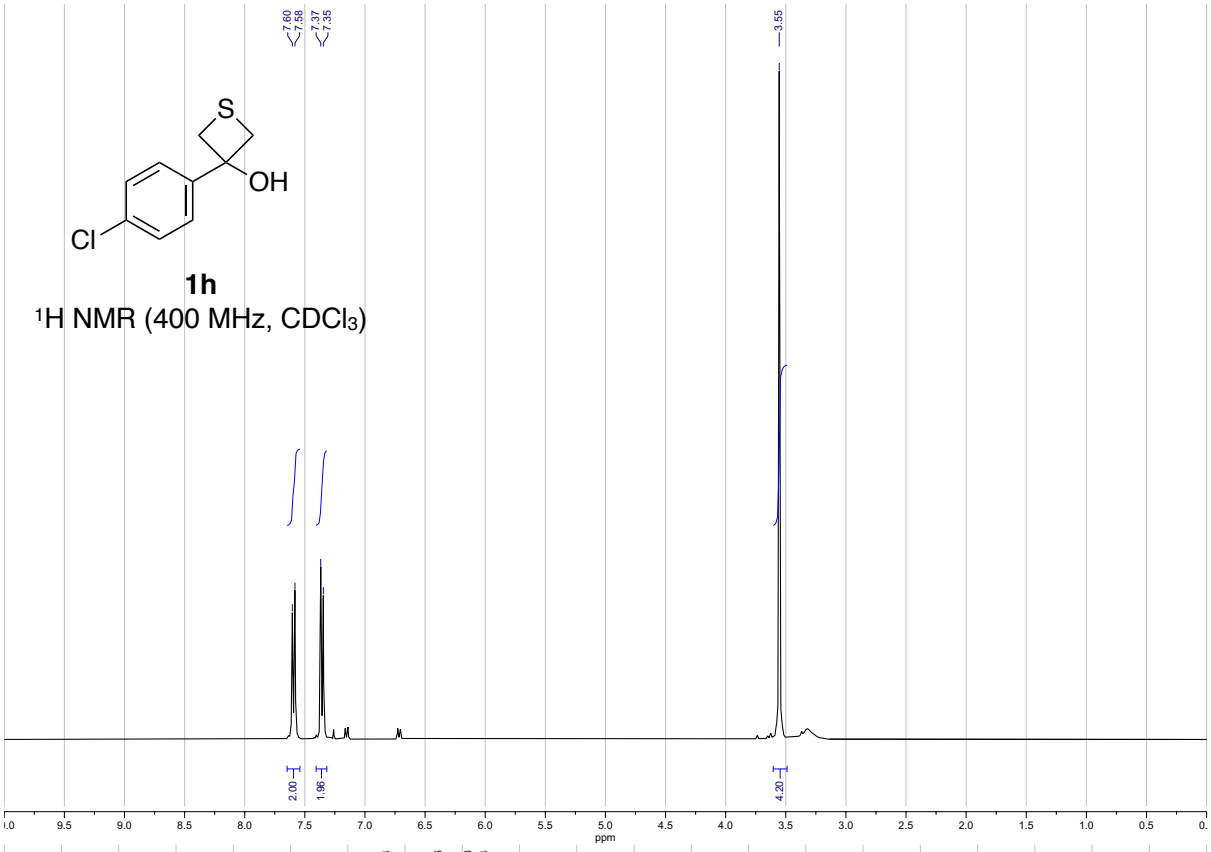
1g

^{1}H NMR (400 MHz, $CDCl_3$)

1g

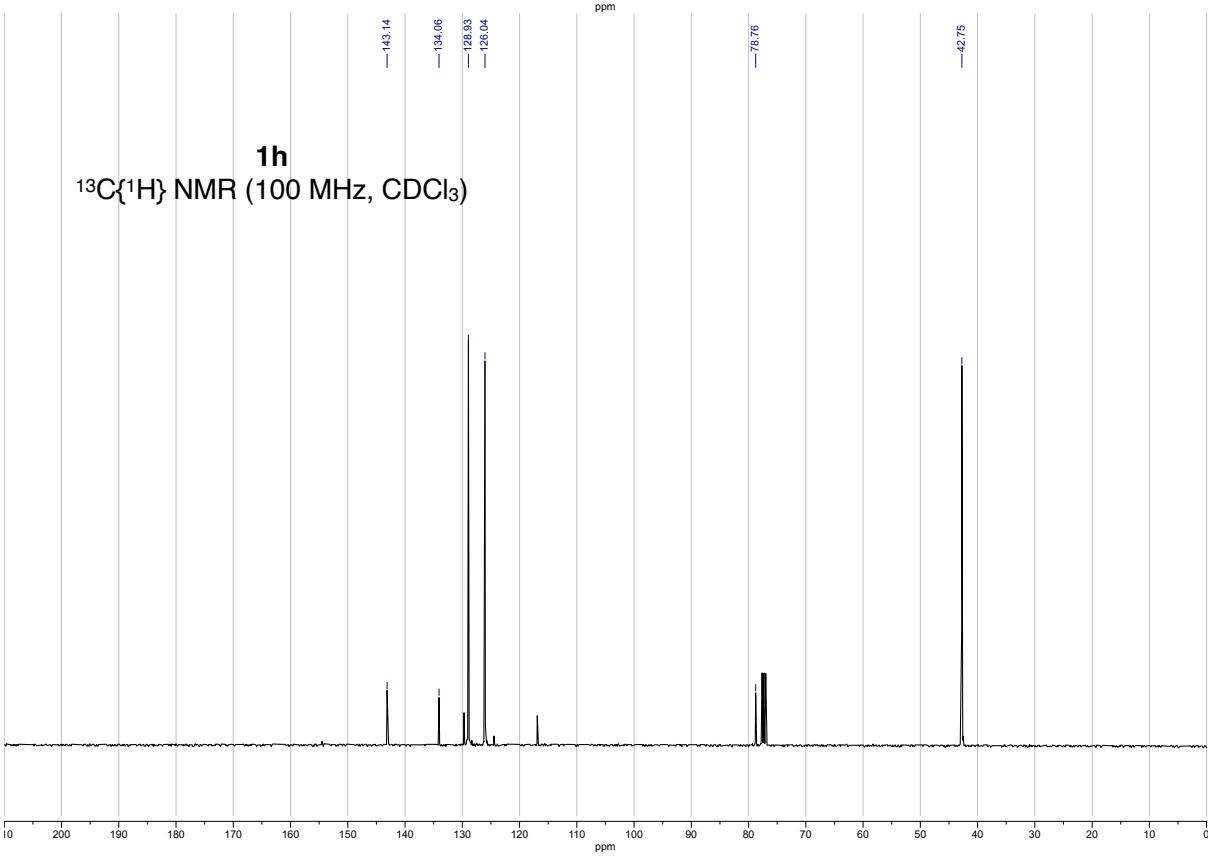
$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$)





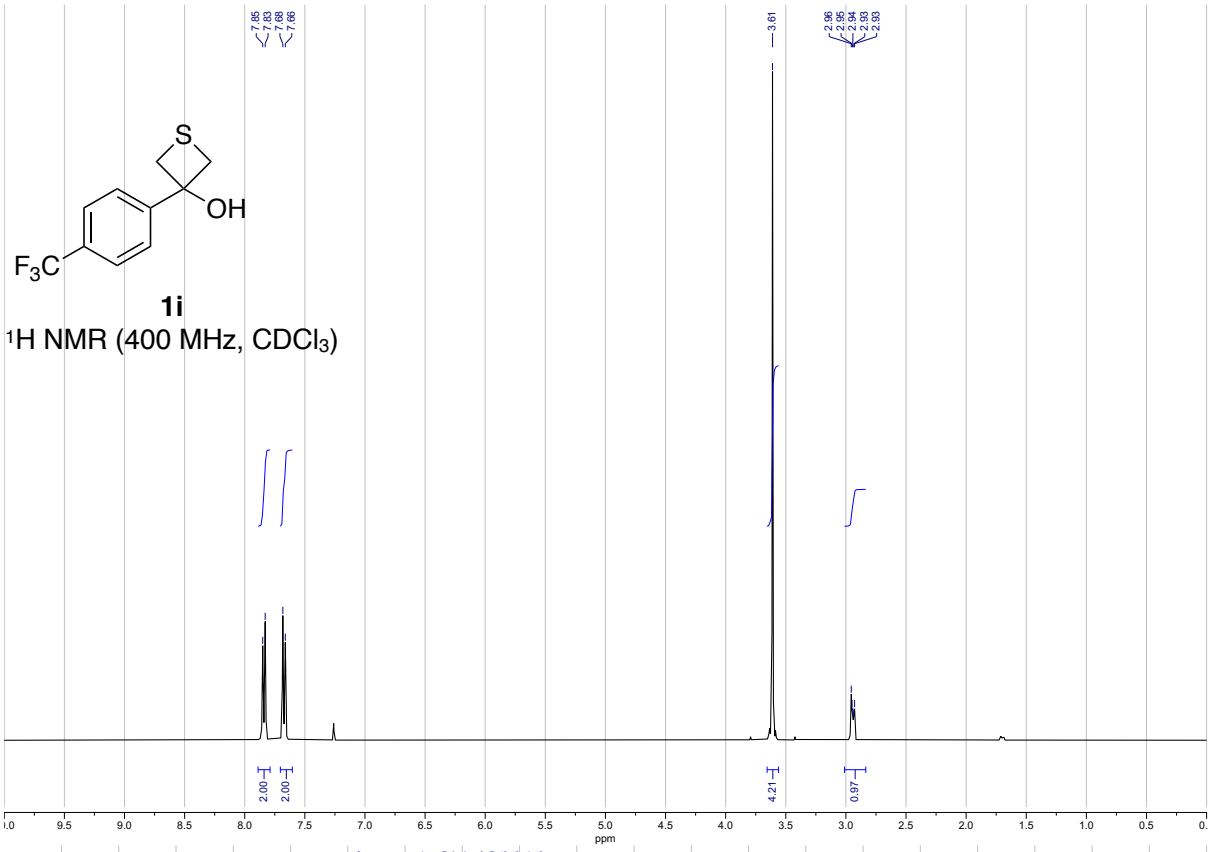
1h

^{1}H NMR (400 MHz, $CDCl_3$)



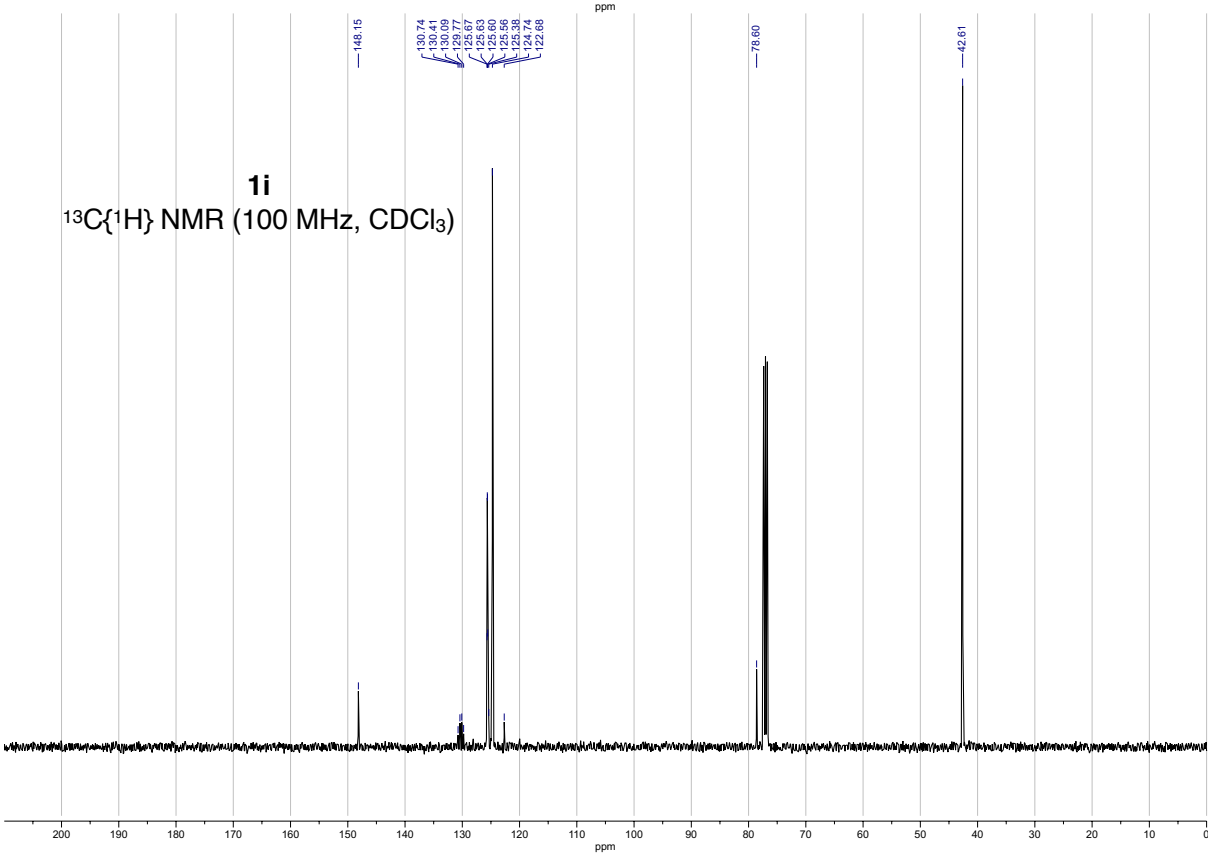
1h

$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$)



1i

^{1}H NMR (400 MHz, $CDCl_3$)

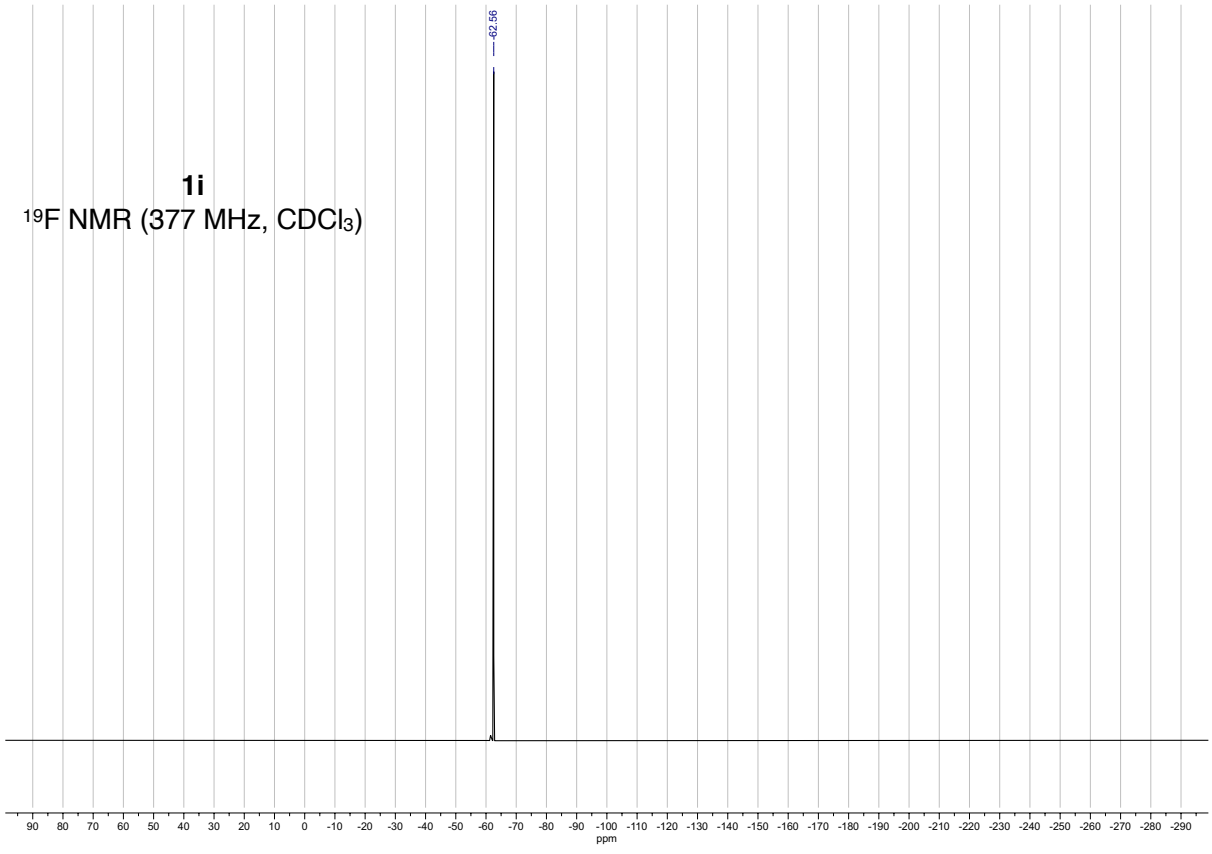


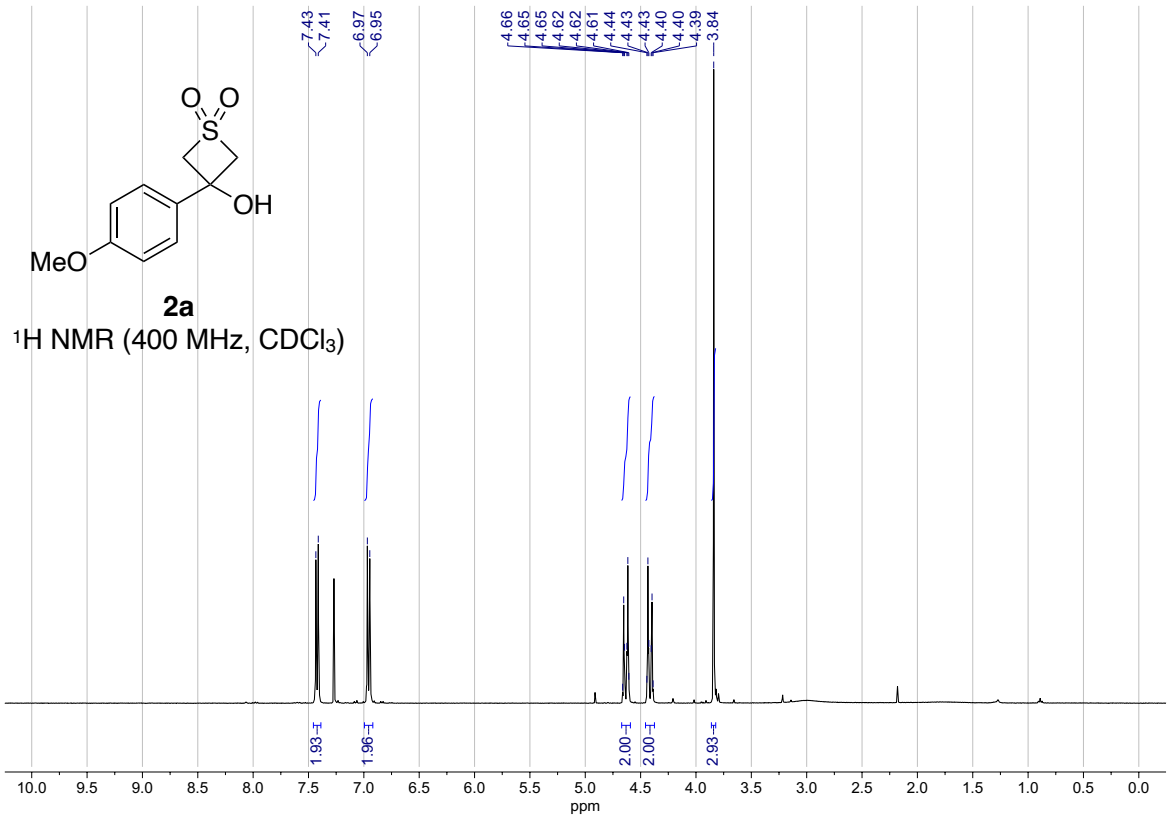
1i

$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$)

1i

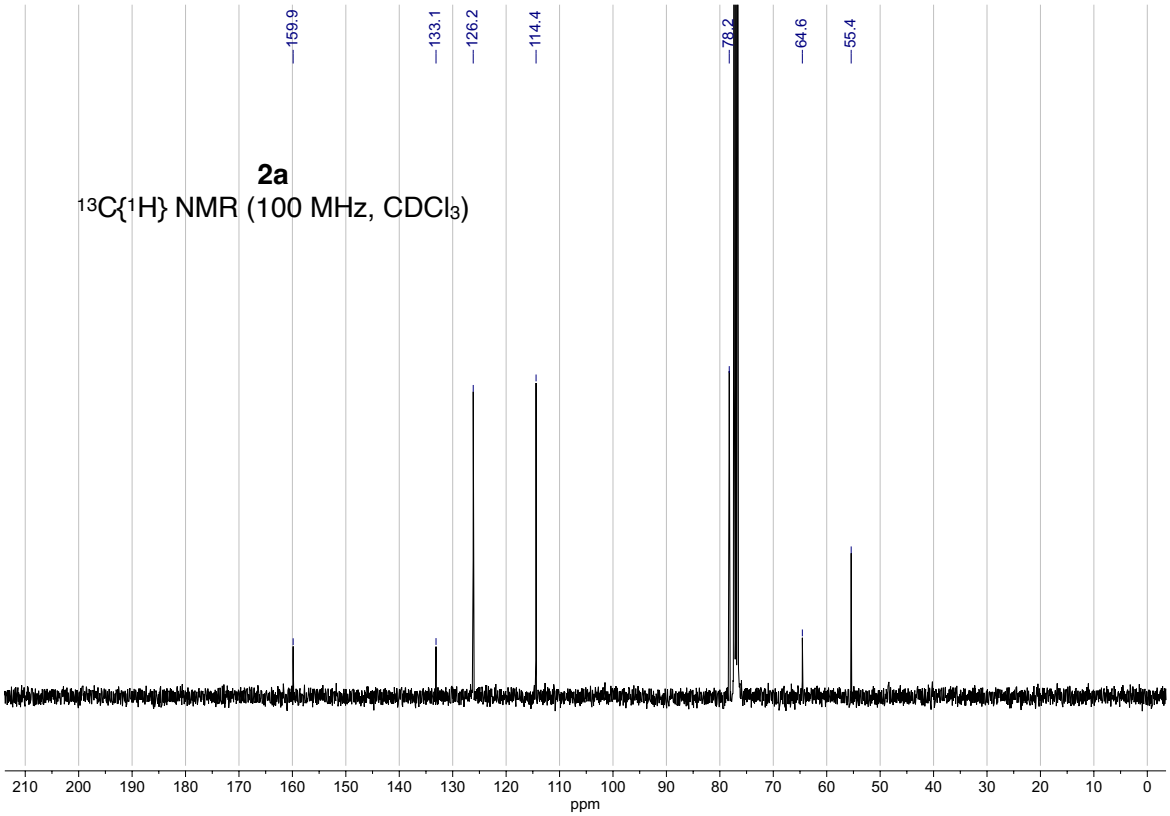
^{19}F NMR (377 MHz, $CDCl_3$)





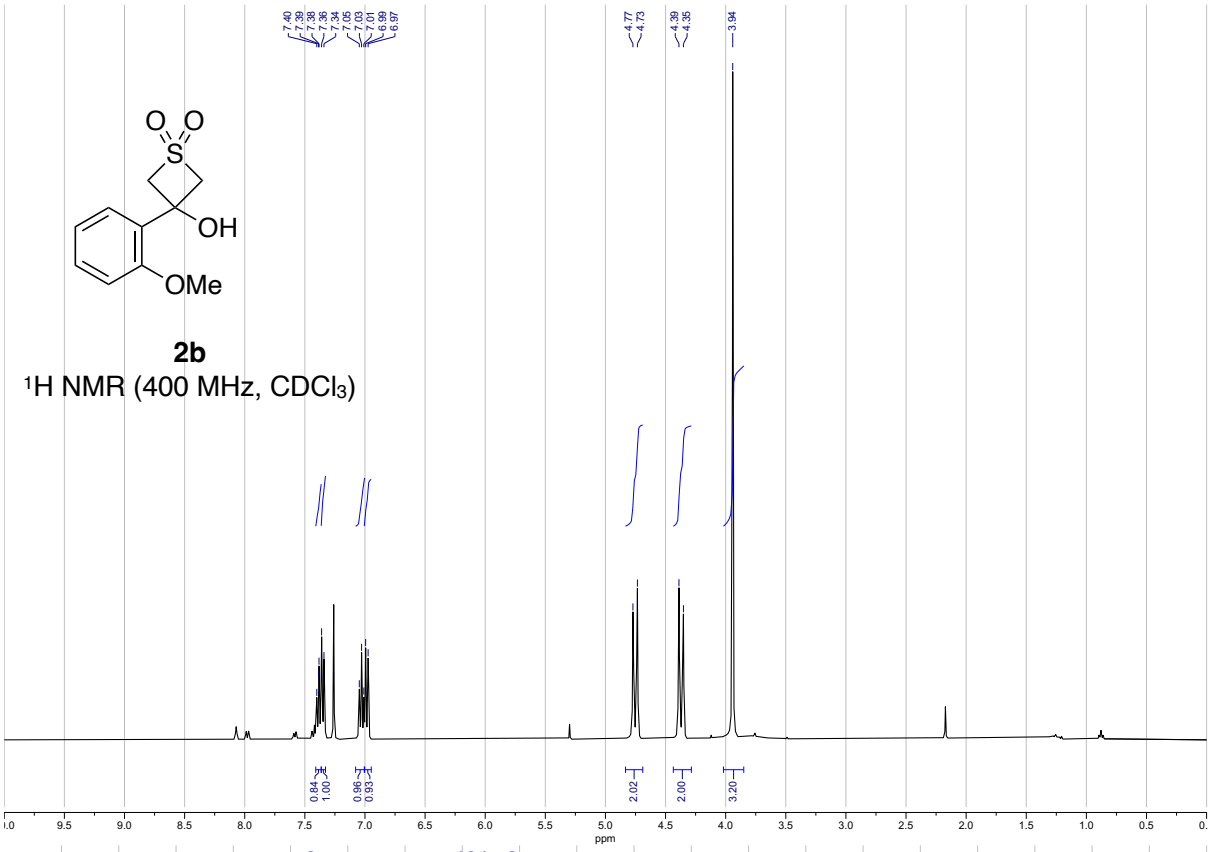
2a

^{1}H NMR (400 MHz, $CDCl_3$)



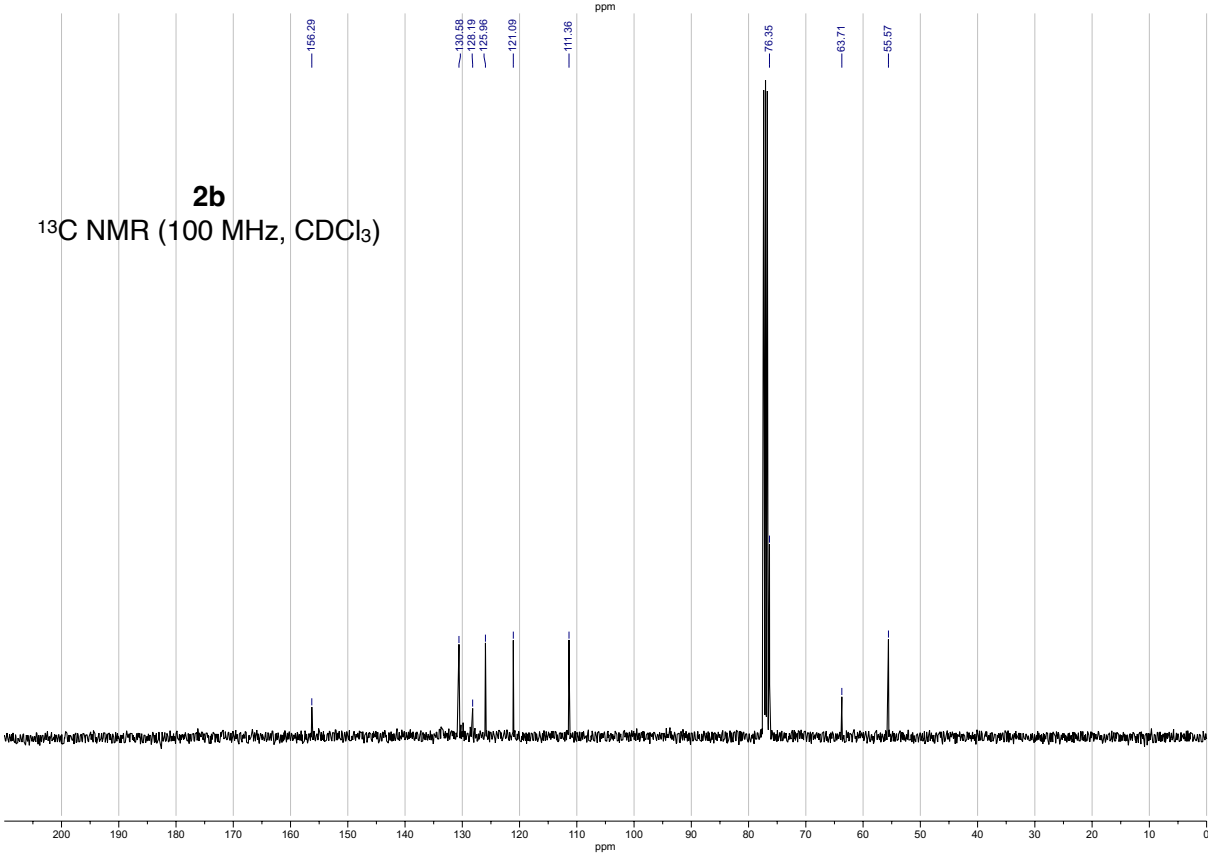
2a

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)



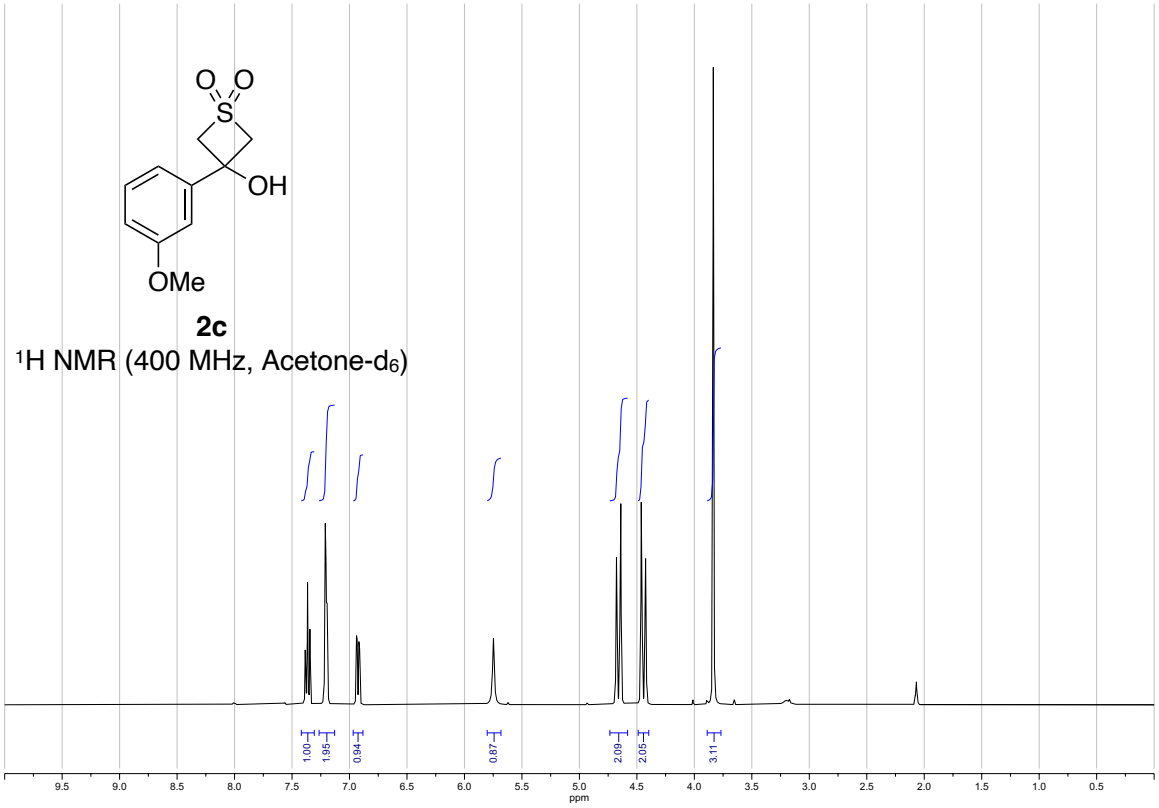
2b

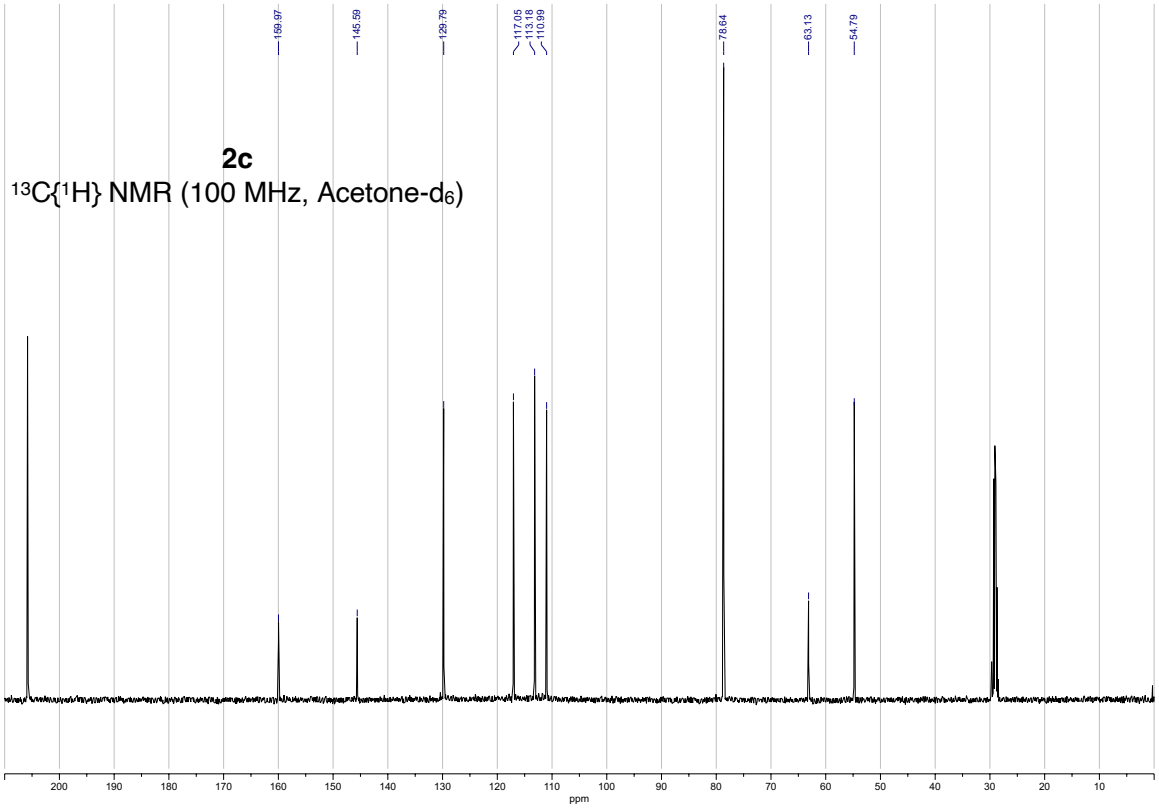
^{1}H NMR (400 MHz, $CDCl_3$)

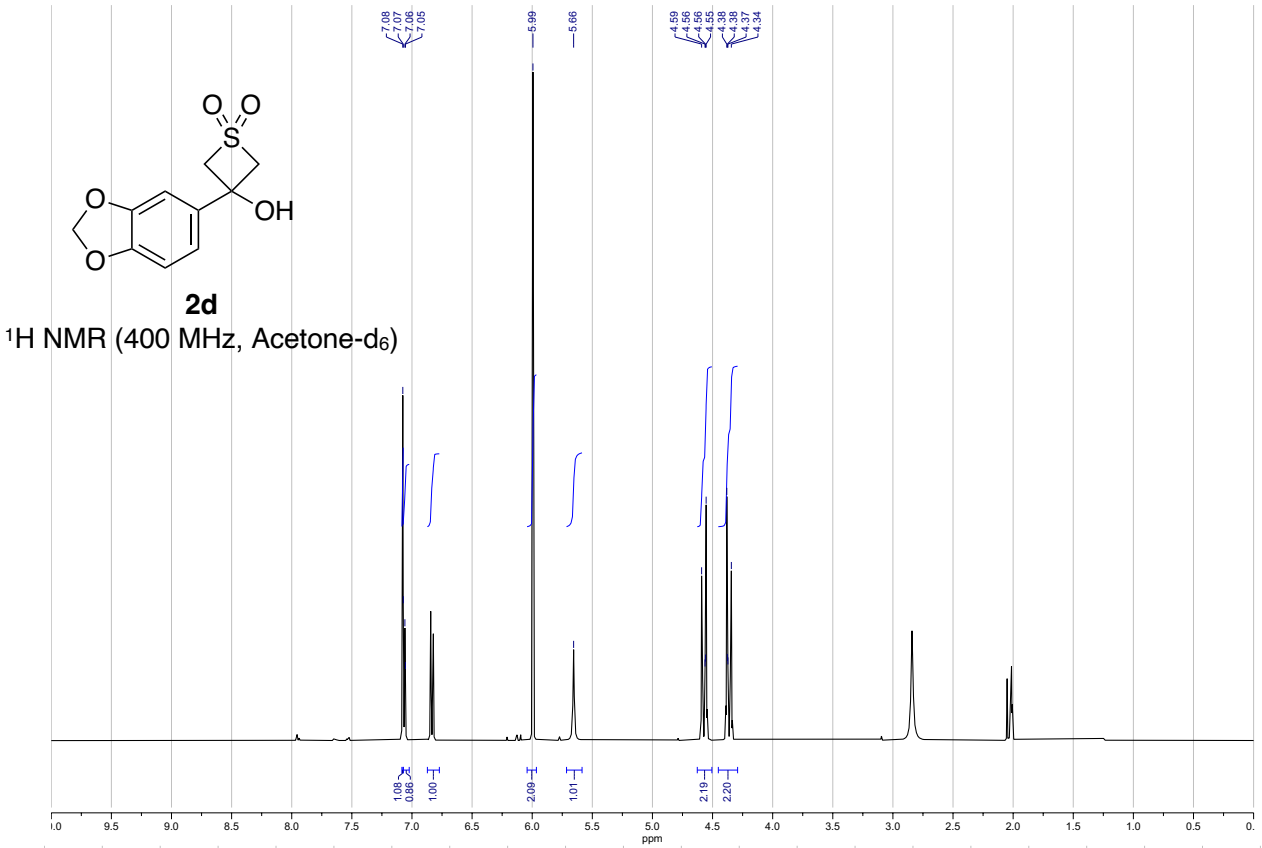


2b

^{13}C NMR (100 MHz, $CDCl_3$)

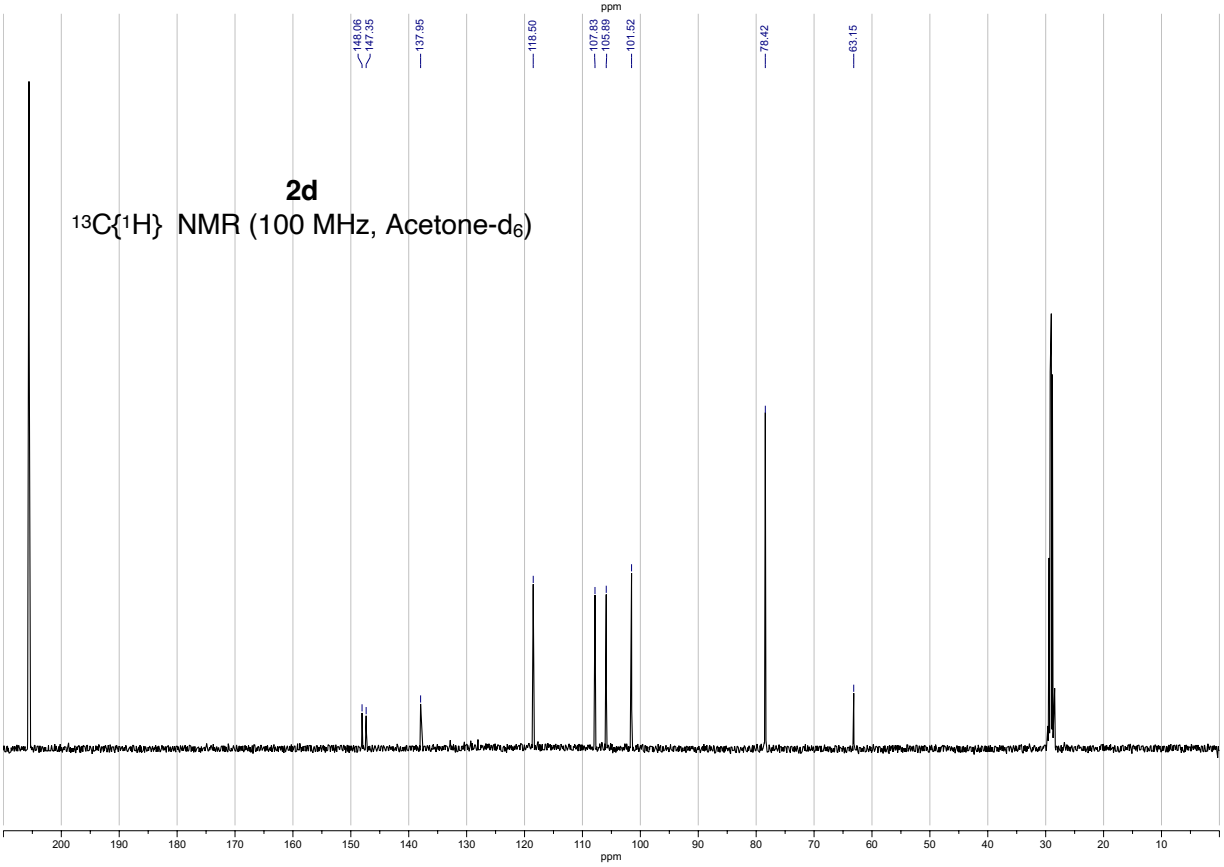

OH
OMe
2c
^{1}H NMR (400 MHz, Acetone-d$_6$)
1.00
1.95
0.94
0.87
2.09
2.05
3.11
ppm


169.97
145.59
129.79
117.05
113.18
110.99
78.64
63.13
54.79
2c
^{13}C{^{1}H} NMR (100 MHz, Acetone-d$_6$)
ppm



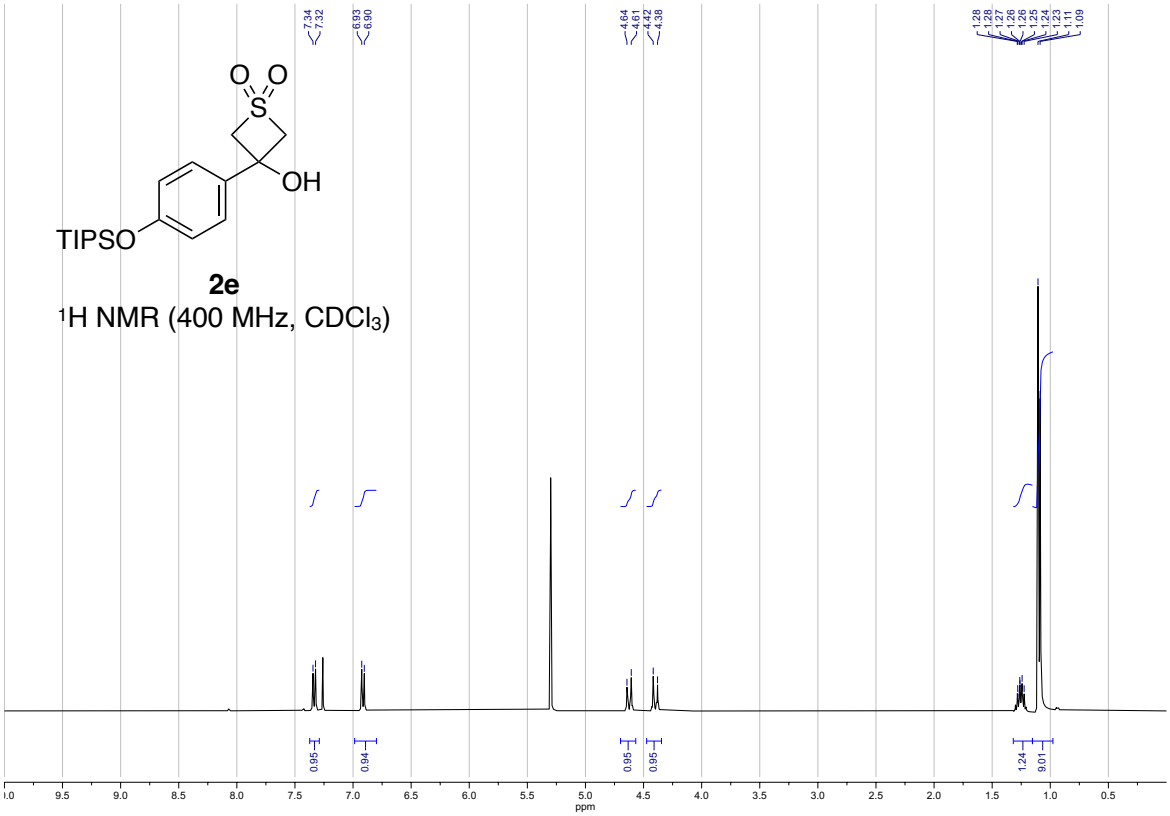
2d

^{1}H NMR (400 MHz, Acetone-d$_6$)



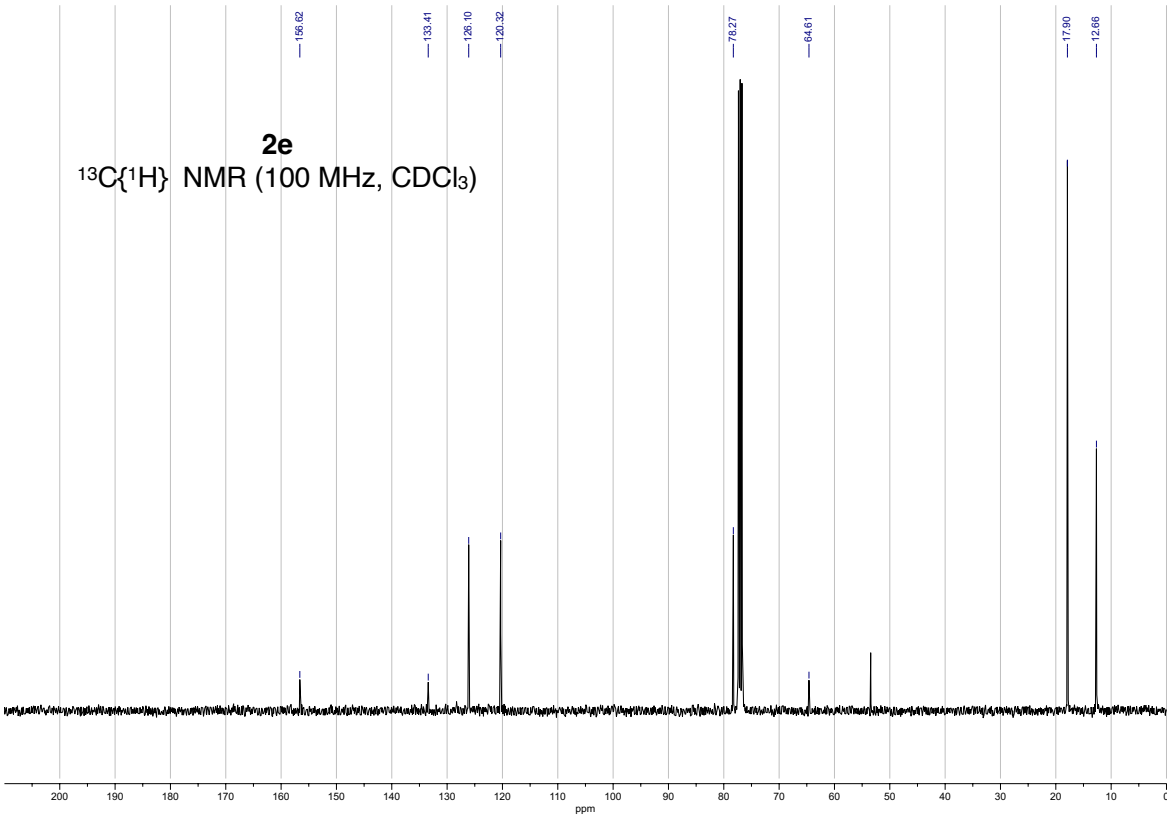
2d

^{13}C{^{1}H} NMR (100 MHz, Acetone-d$_6$)



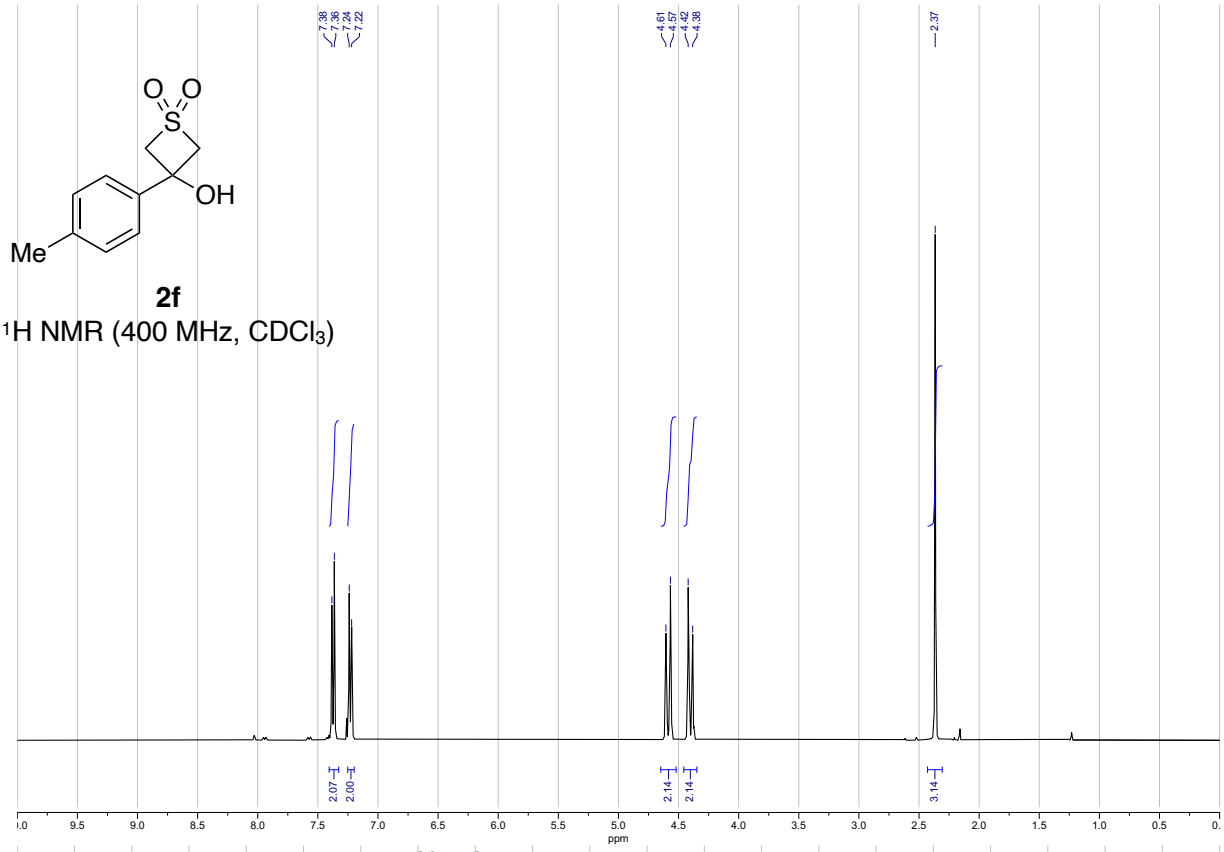
2e

^{1}H NMR (400 MHz, $CDCl_3$)



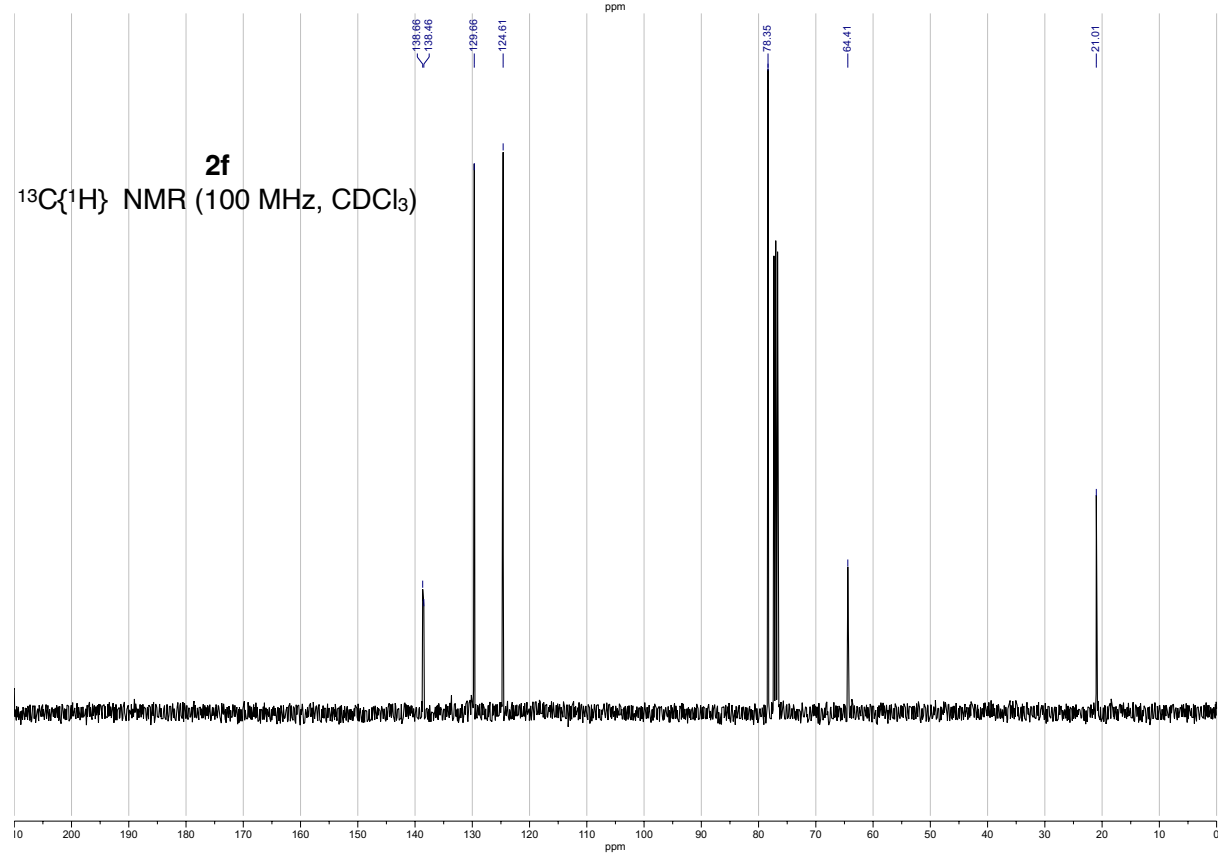
2e

$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$)



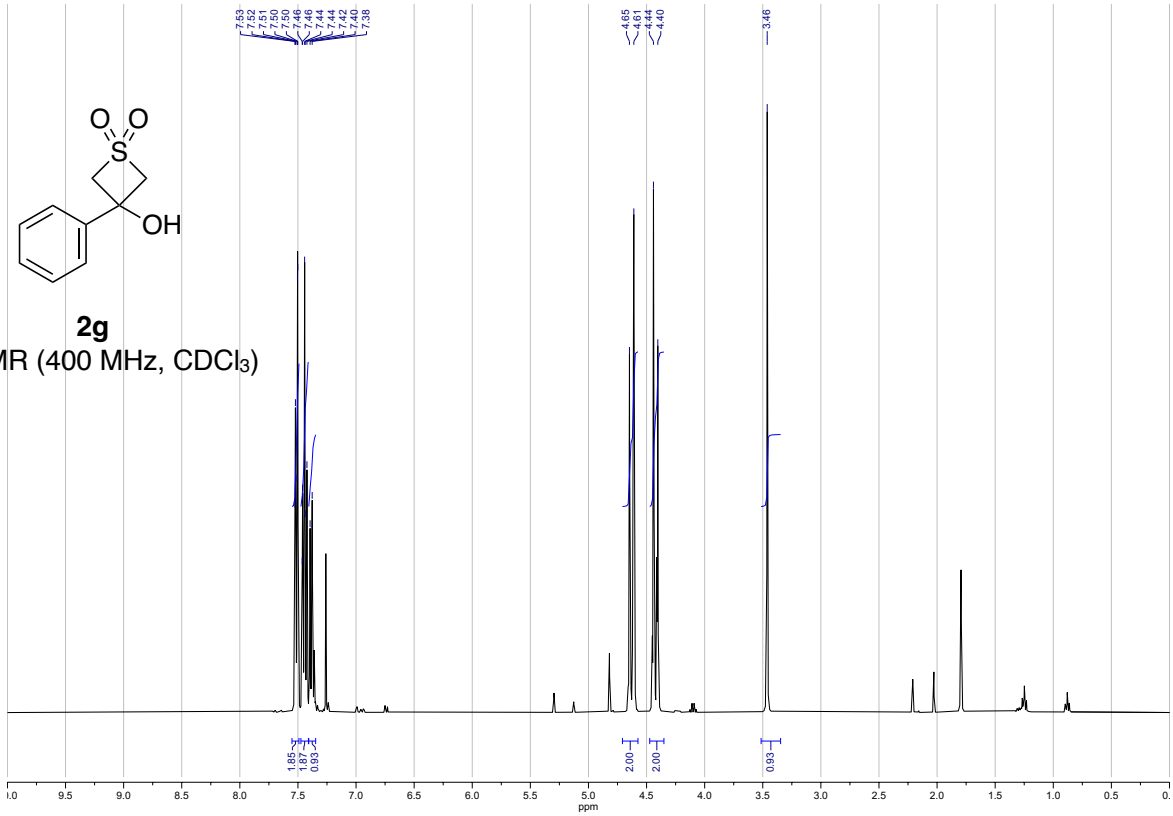
2f

^{1}H NMR (400 MHz, $CDCl_3$)



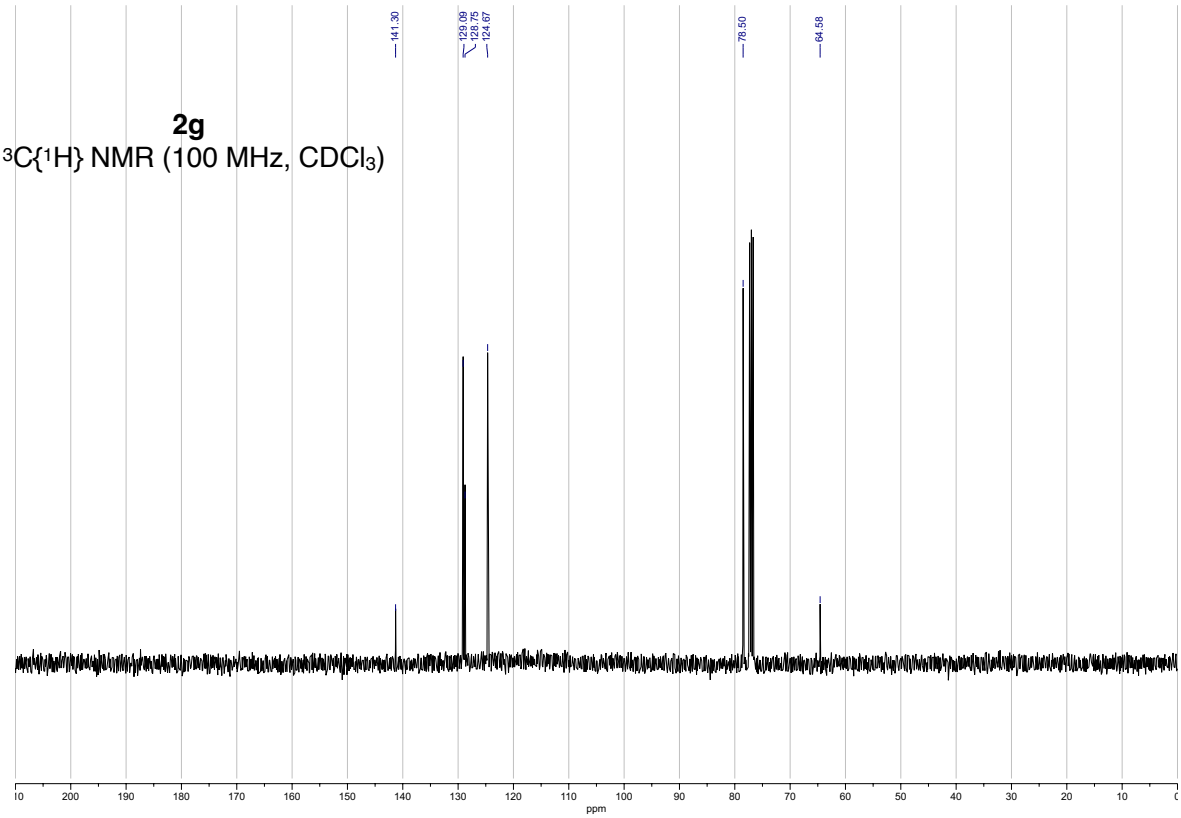
2f

$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$)



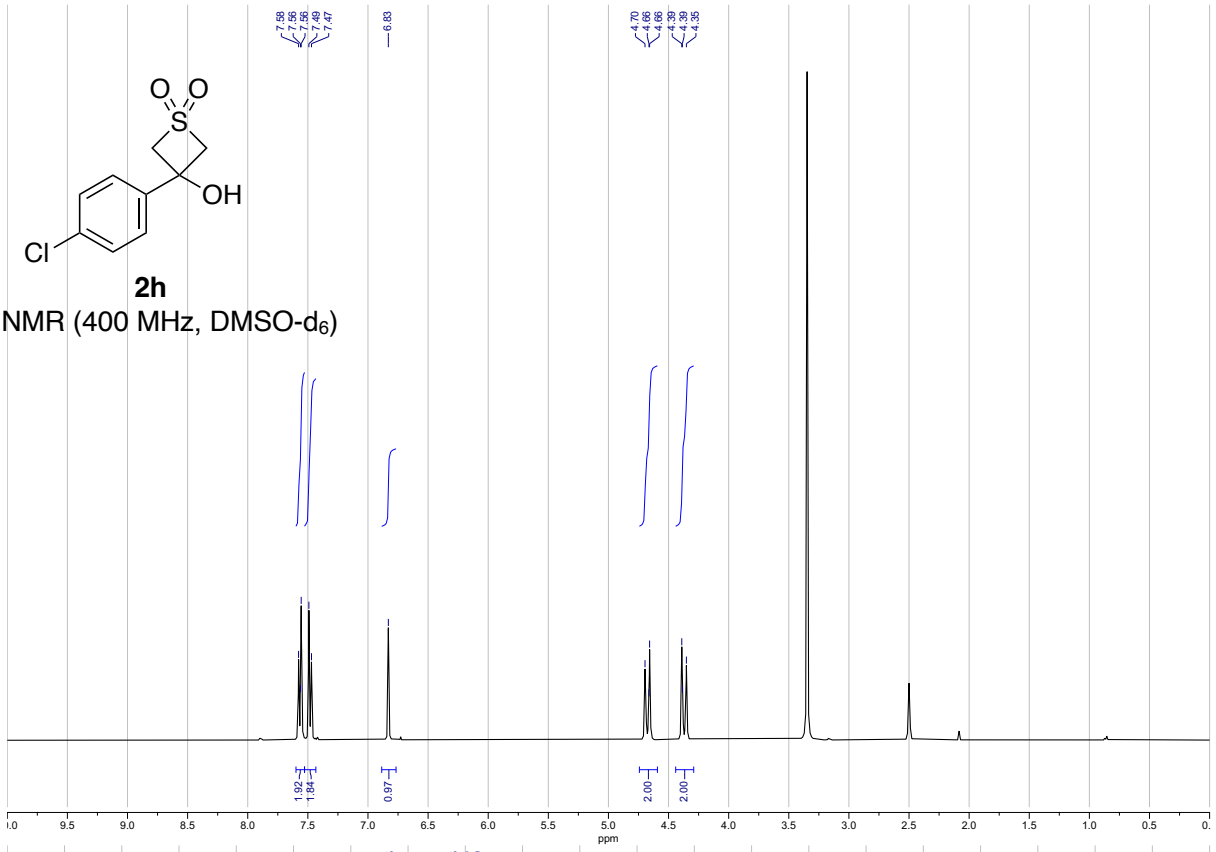
2g

^{1}H NMR (400 MHz, $CDCl_3$)



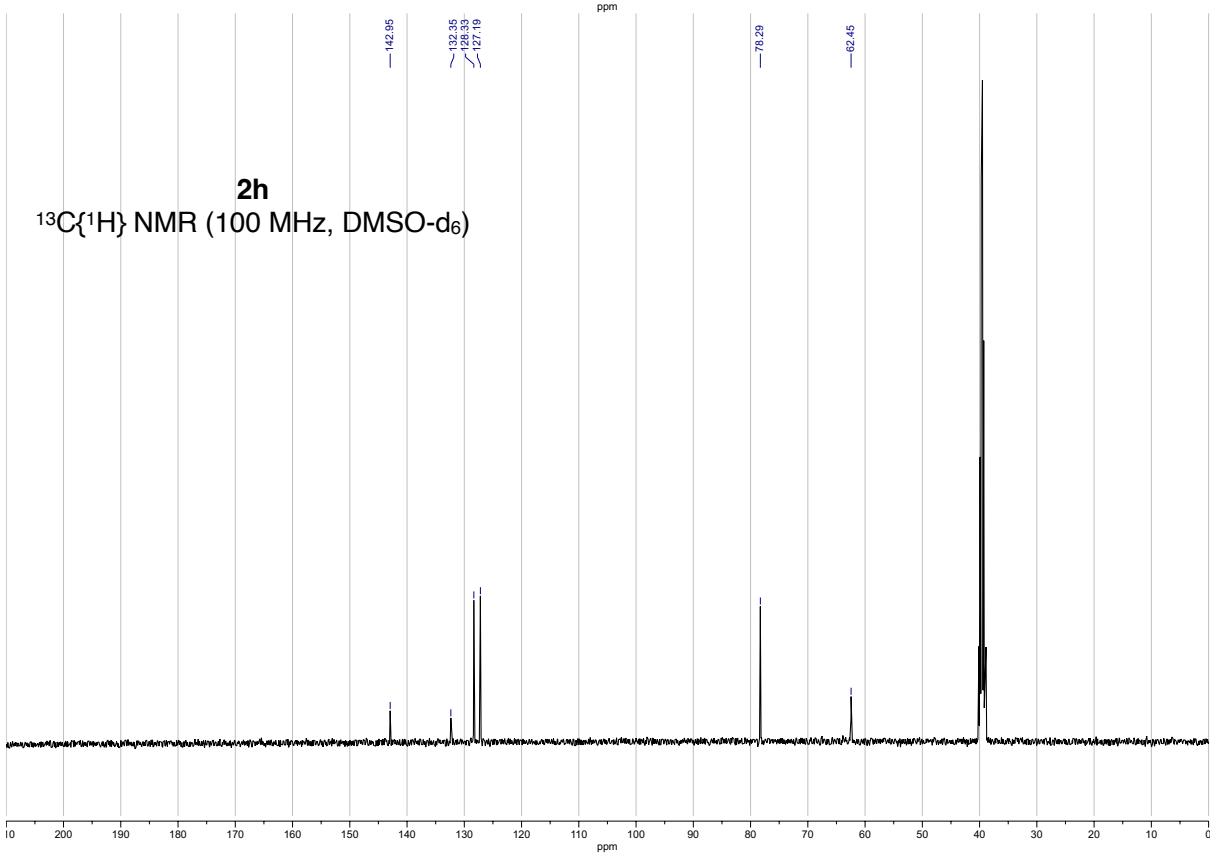
2g

$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$)



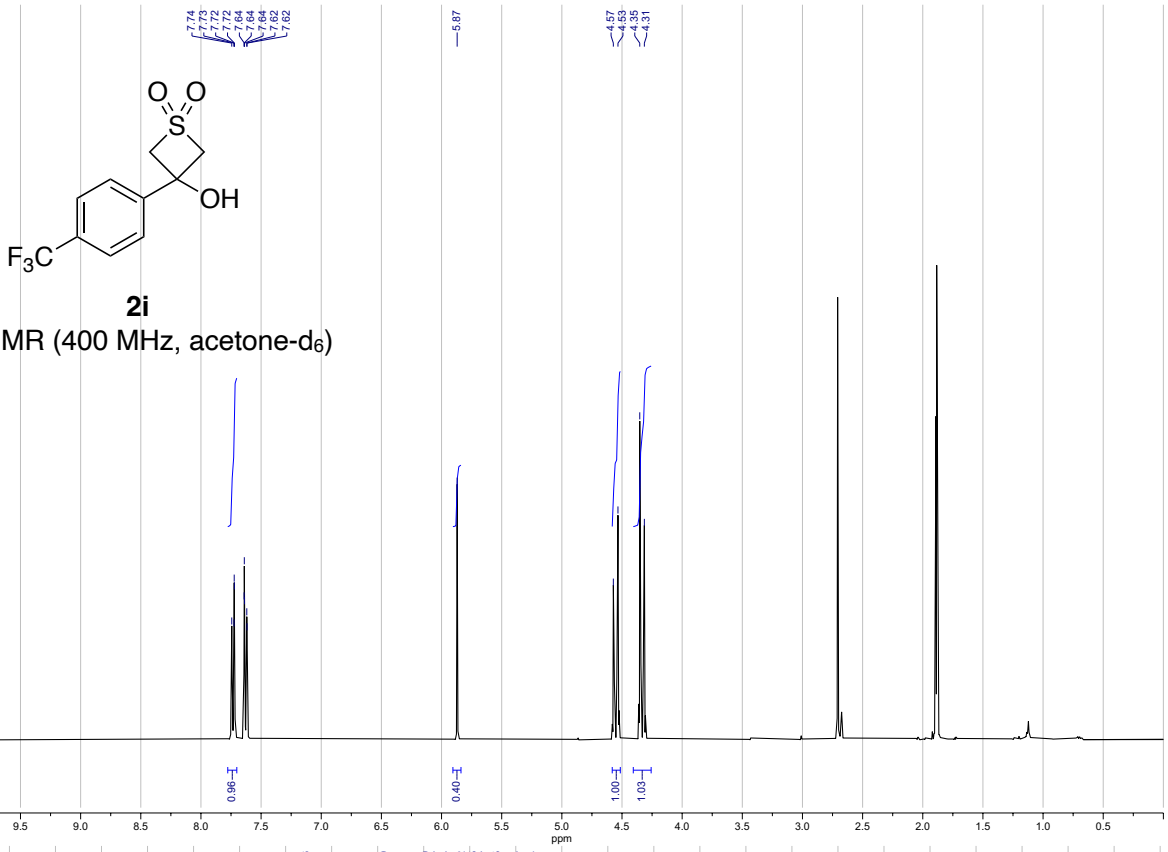
2h

^{1}H NMR (400 MHz, DMSO-d_6)



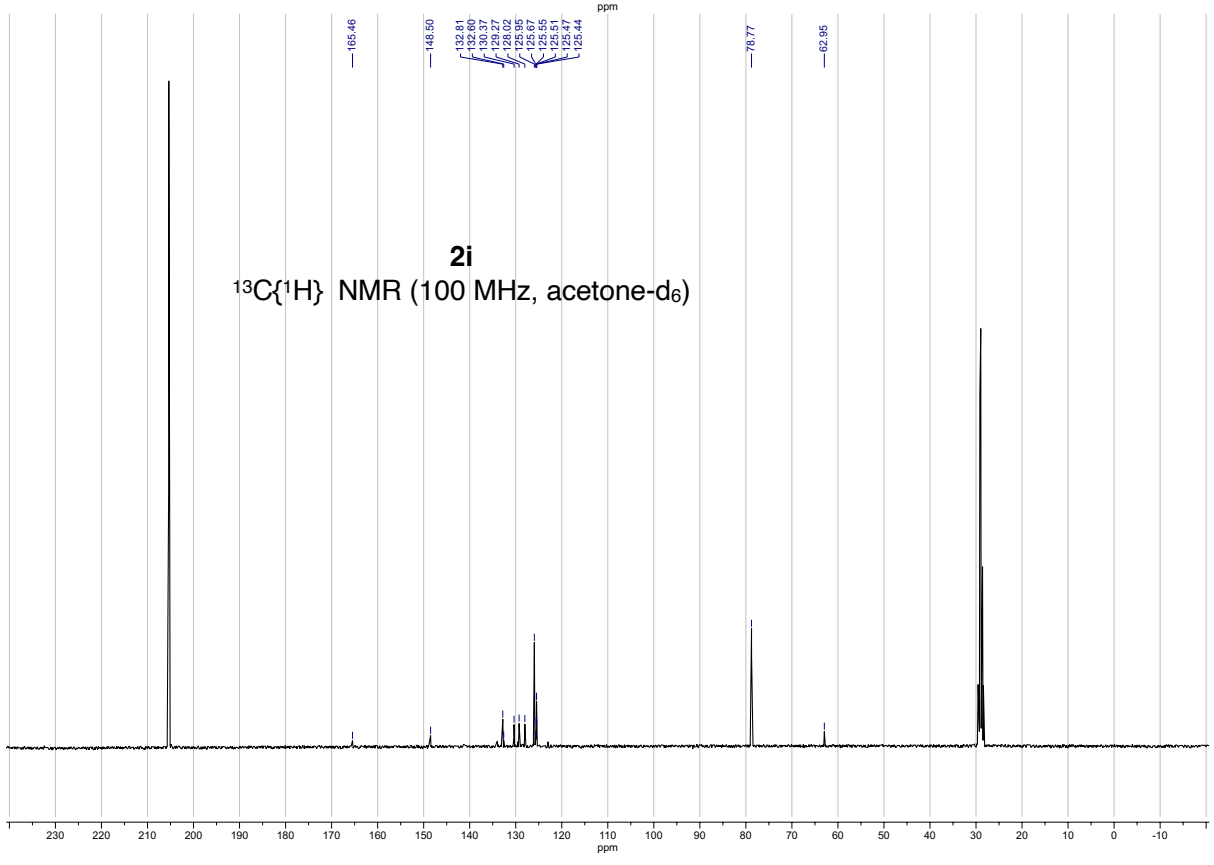
2h

^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6)



2i

^{1}H NMR (400 MHz, acetone-d_6)

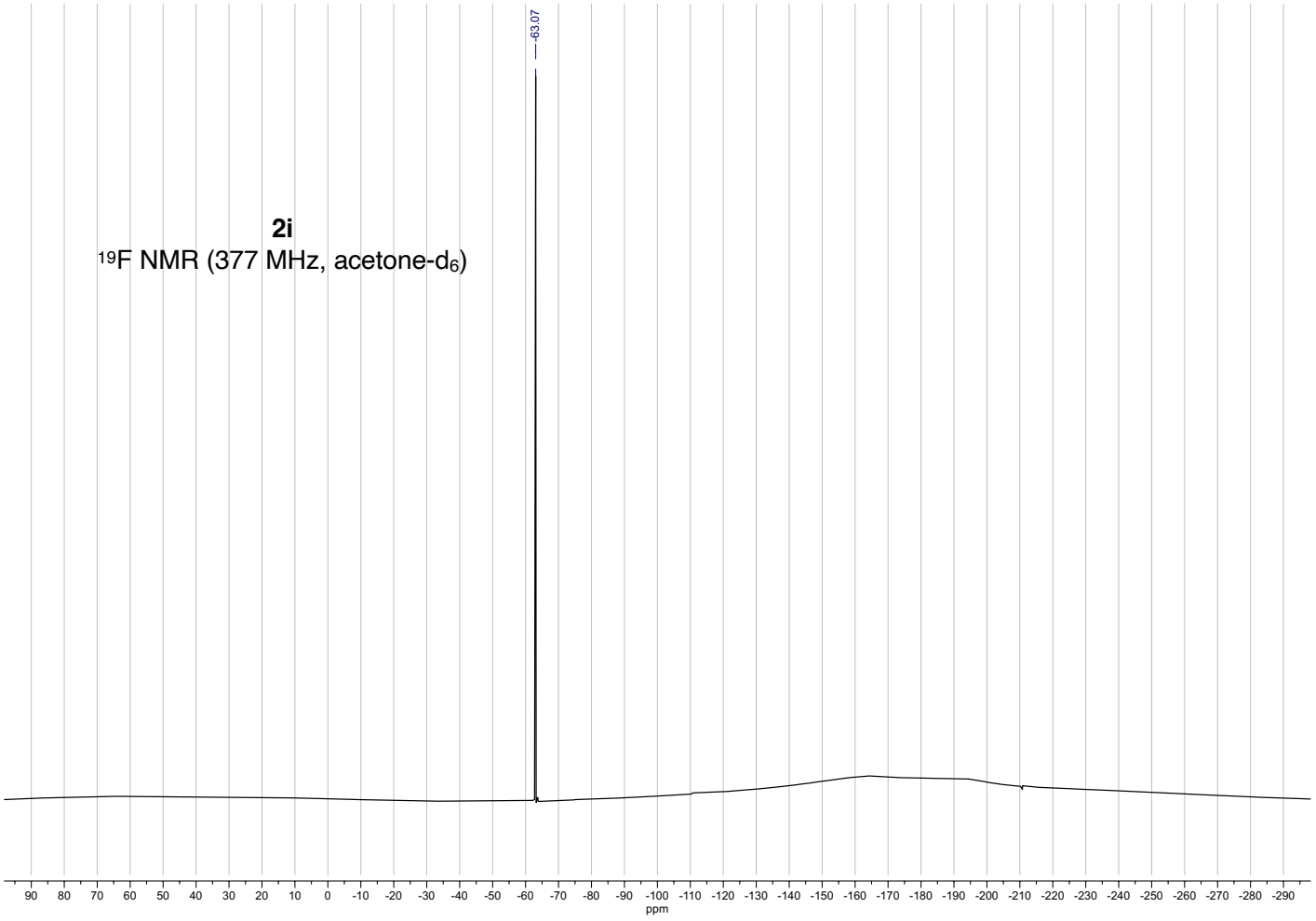


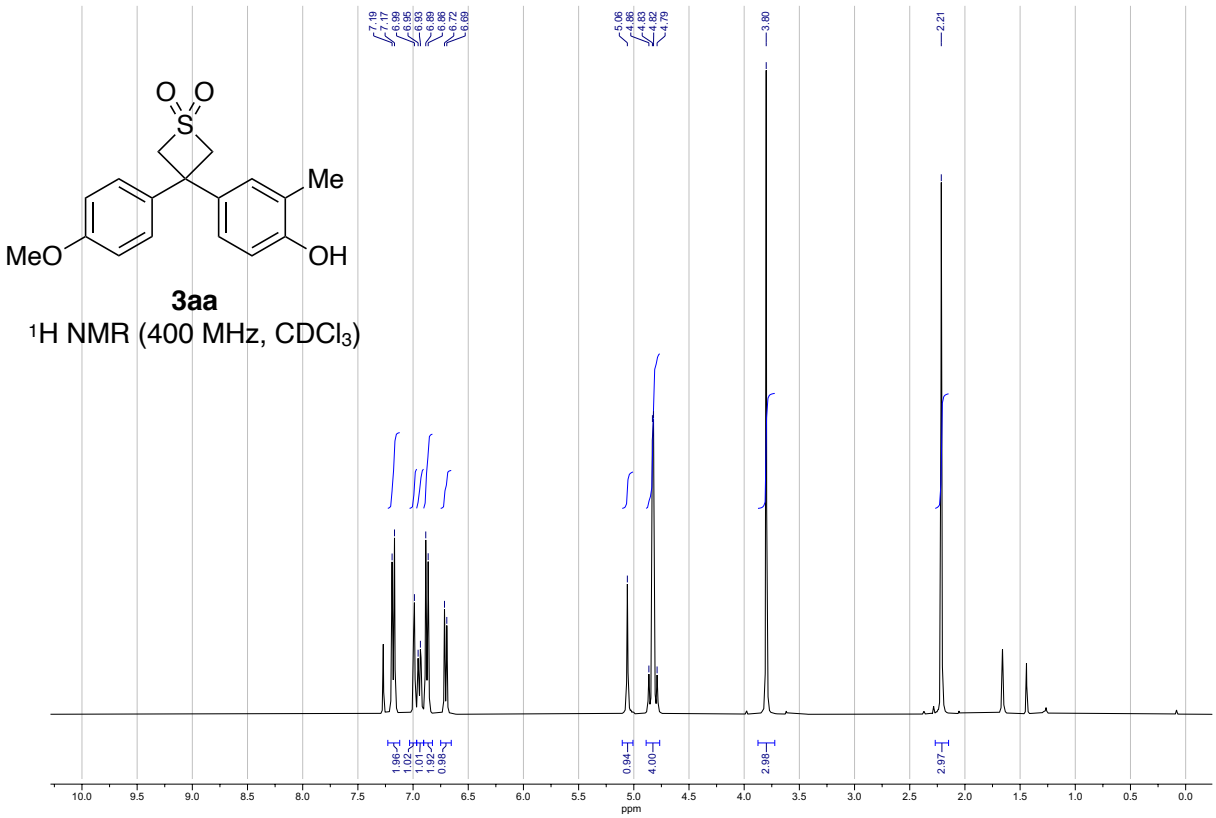
2i

^{13}C{^{1}H} NMR (100 MHz, acetone-d_6)

2i

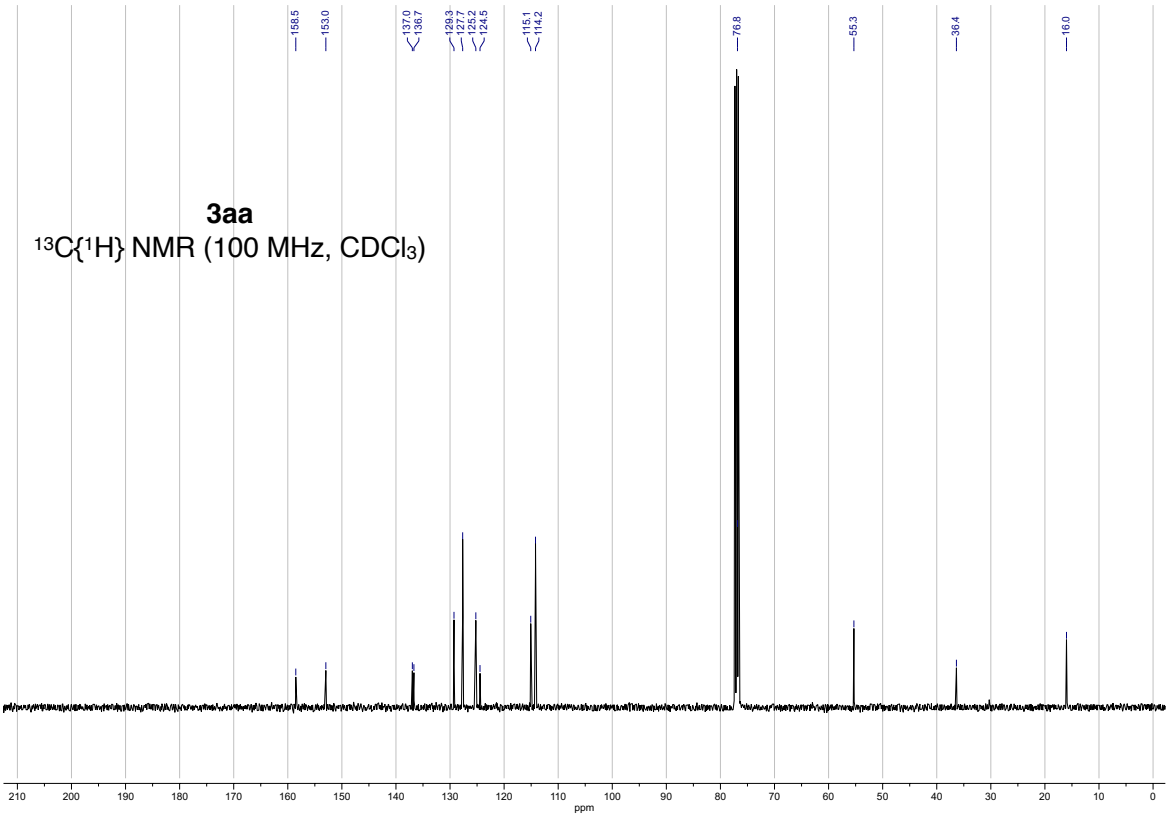
^{19}F NMR (377 MHz, acetone-d_6)





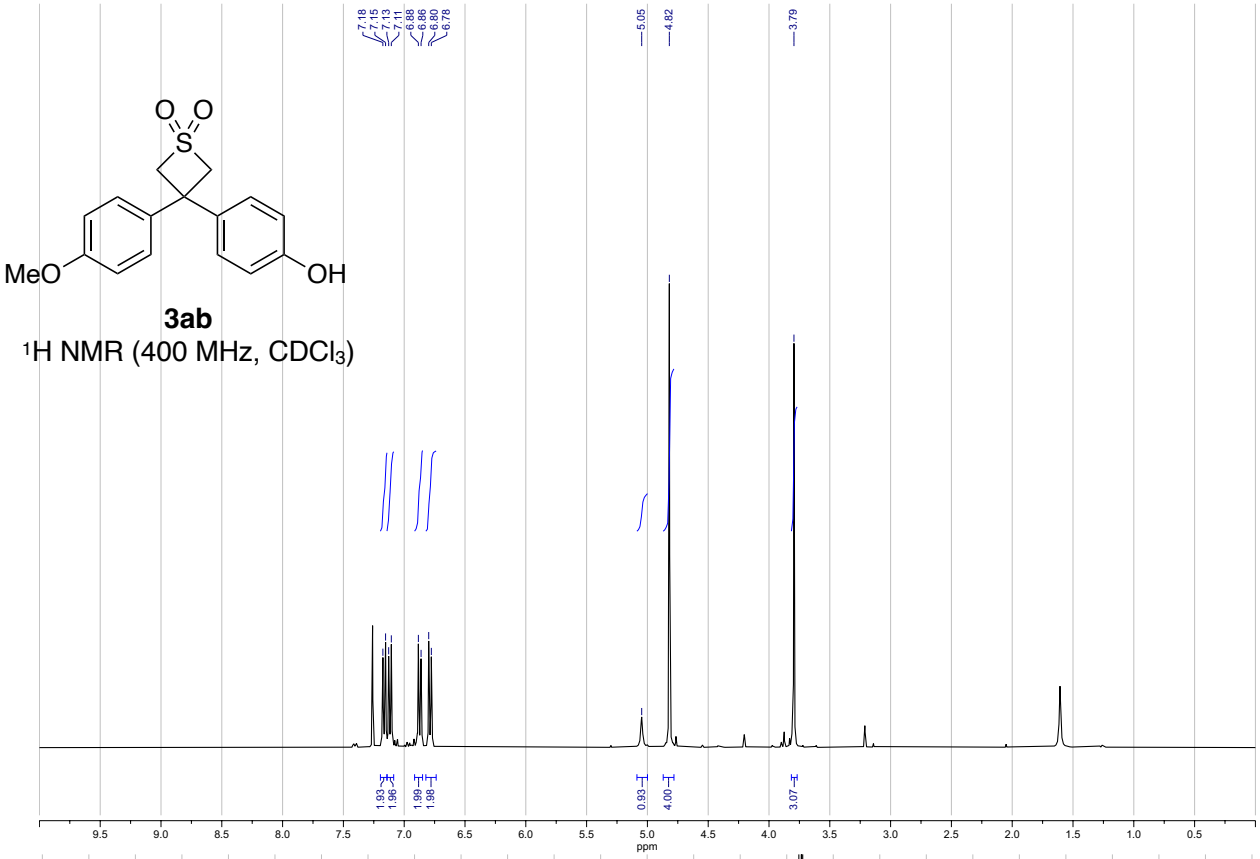
3aa

^{1}H NMR (400 MHz, $CDCl_3$)



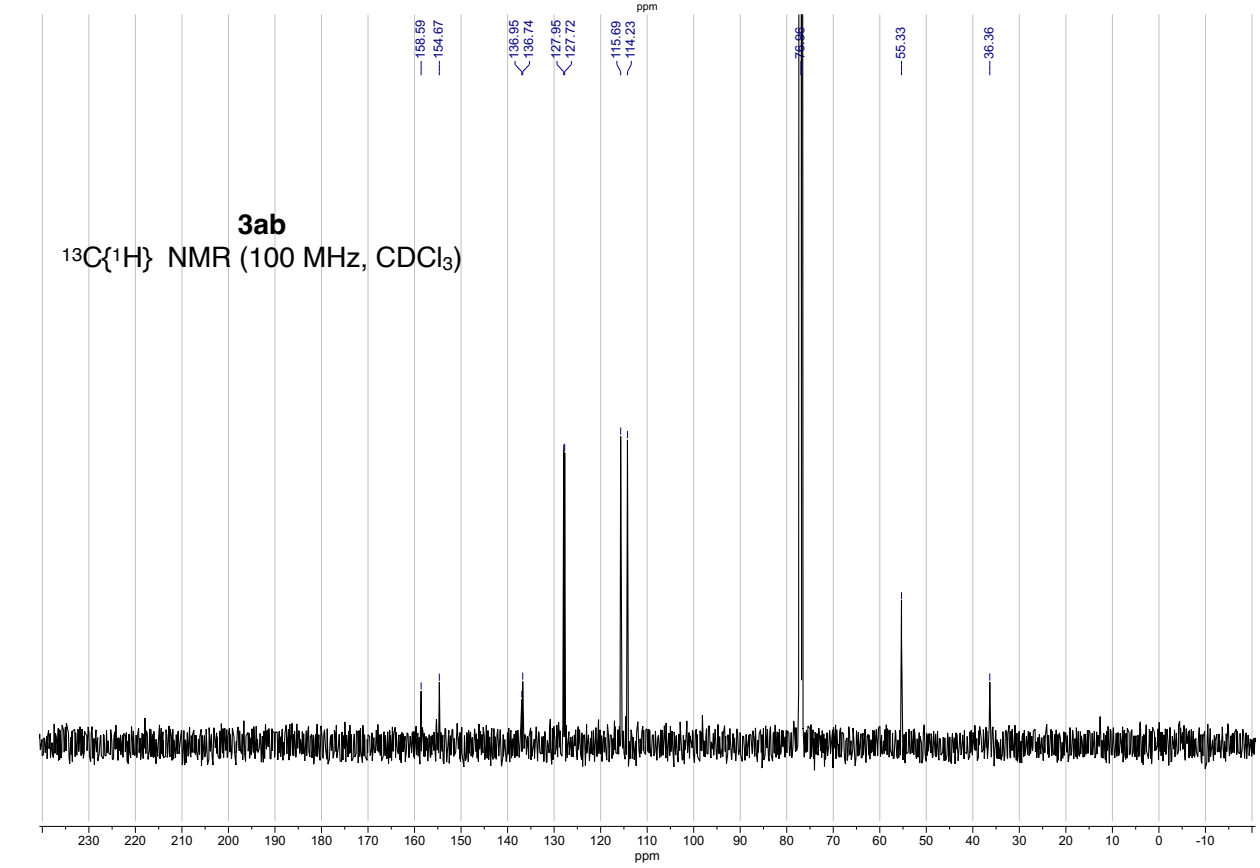
3aa

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)



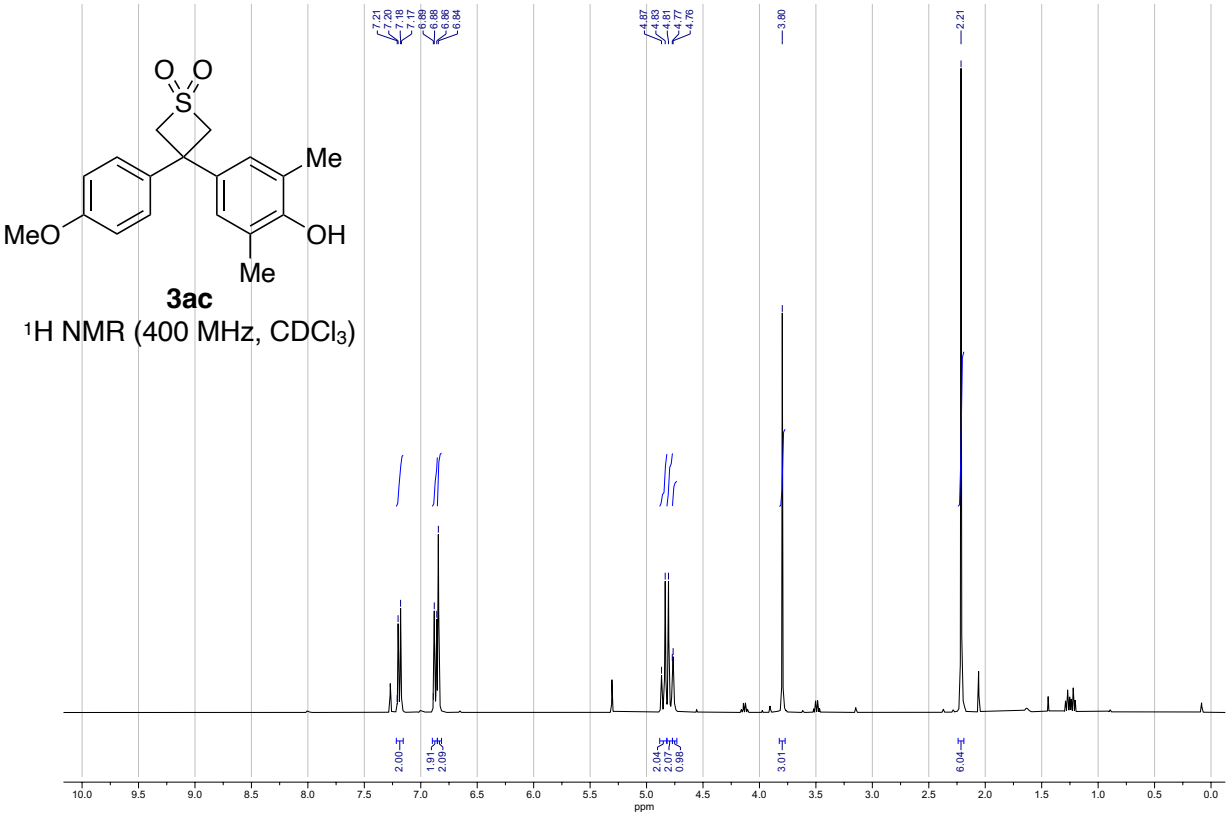
3ab

^{1}H NMR (400 MHz, $CDCl_3$)



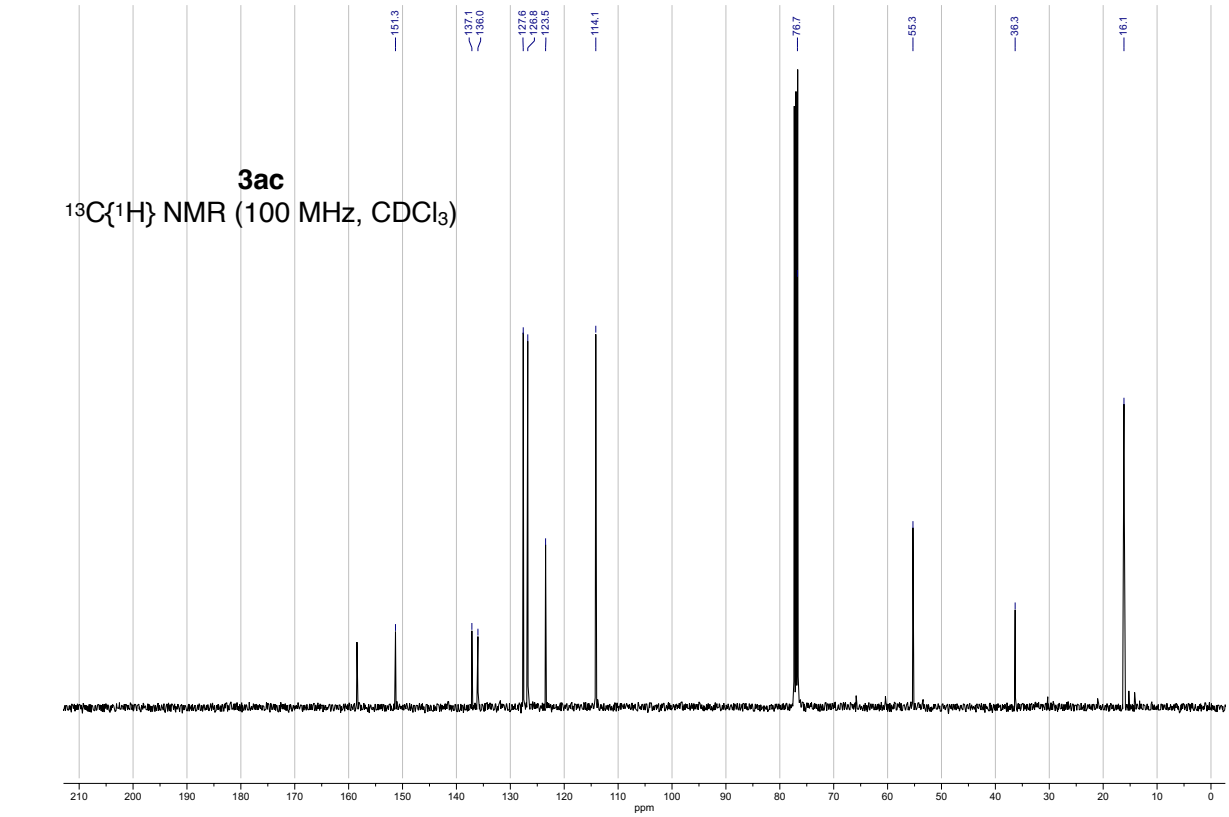
3ab

$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$)



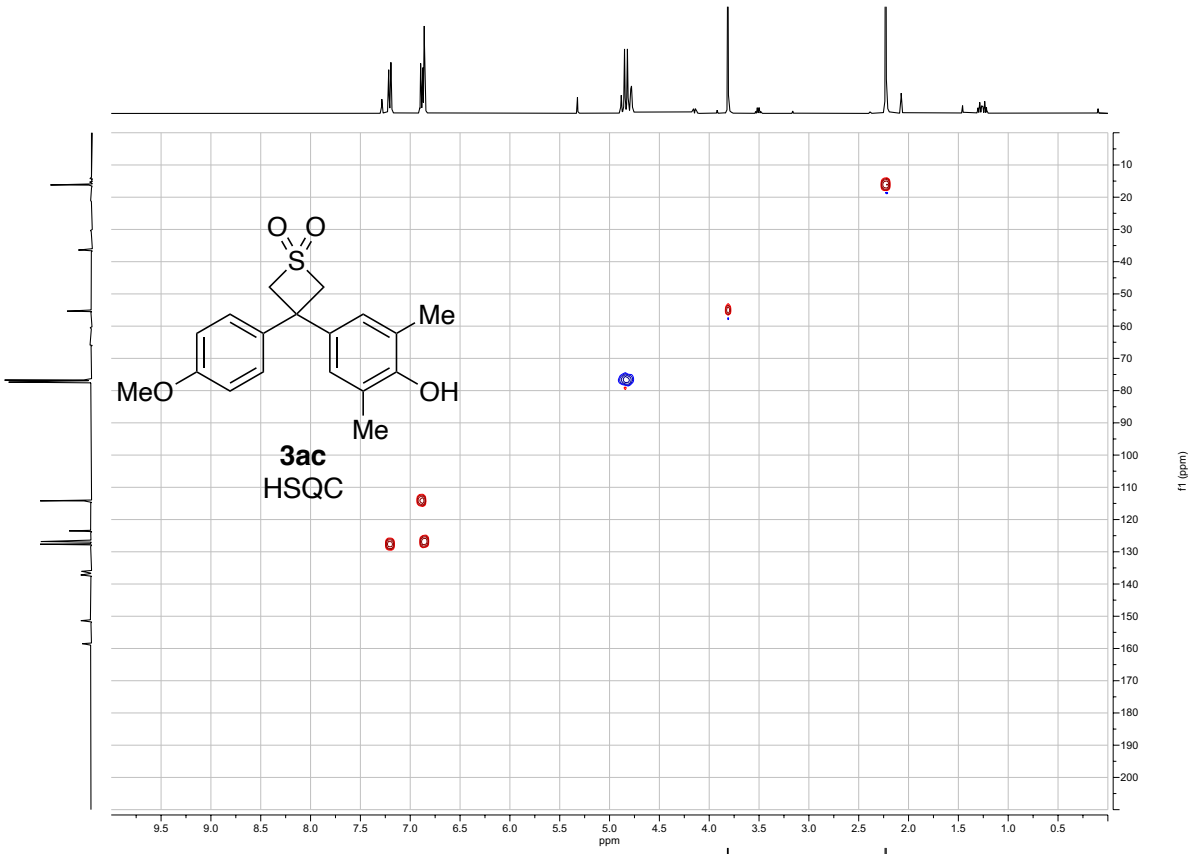
3ac

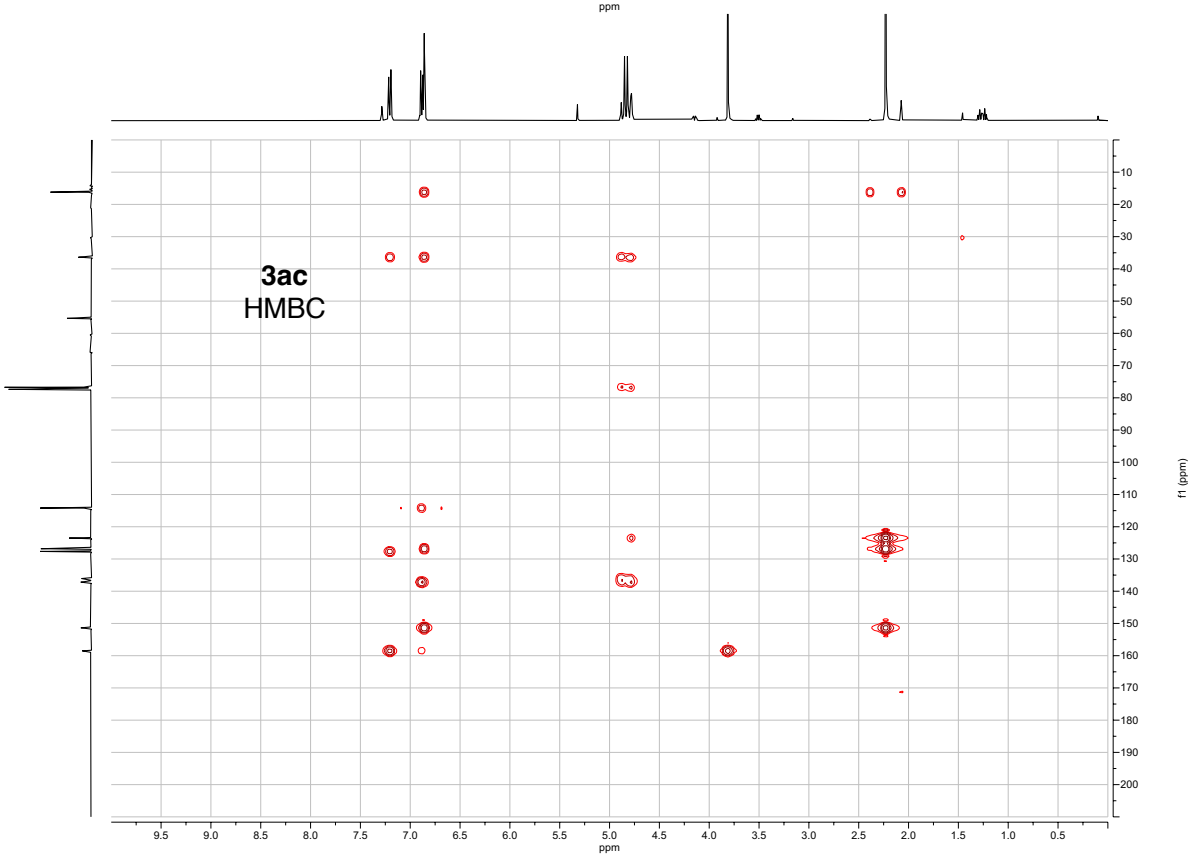
^{1}H NMR (400 MHz, $CDCl_3$)

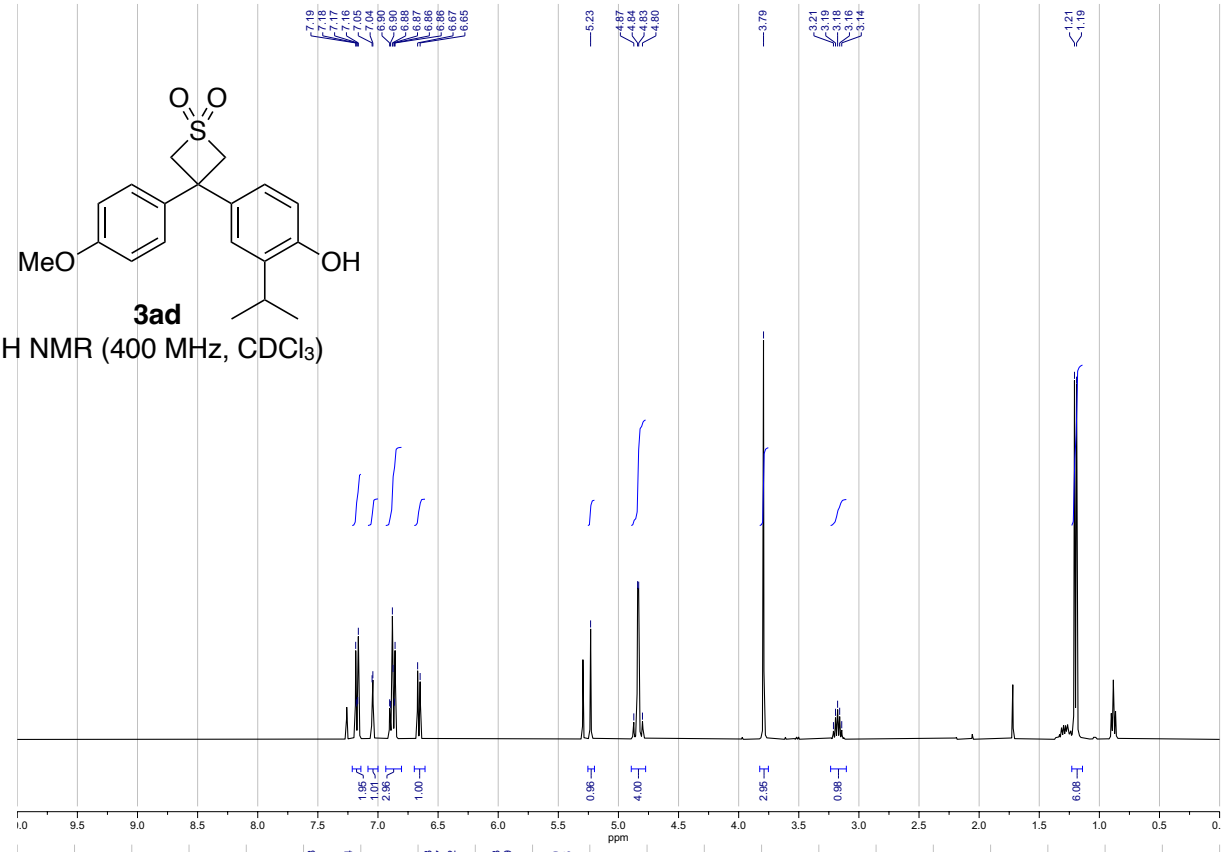


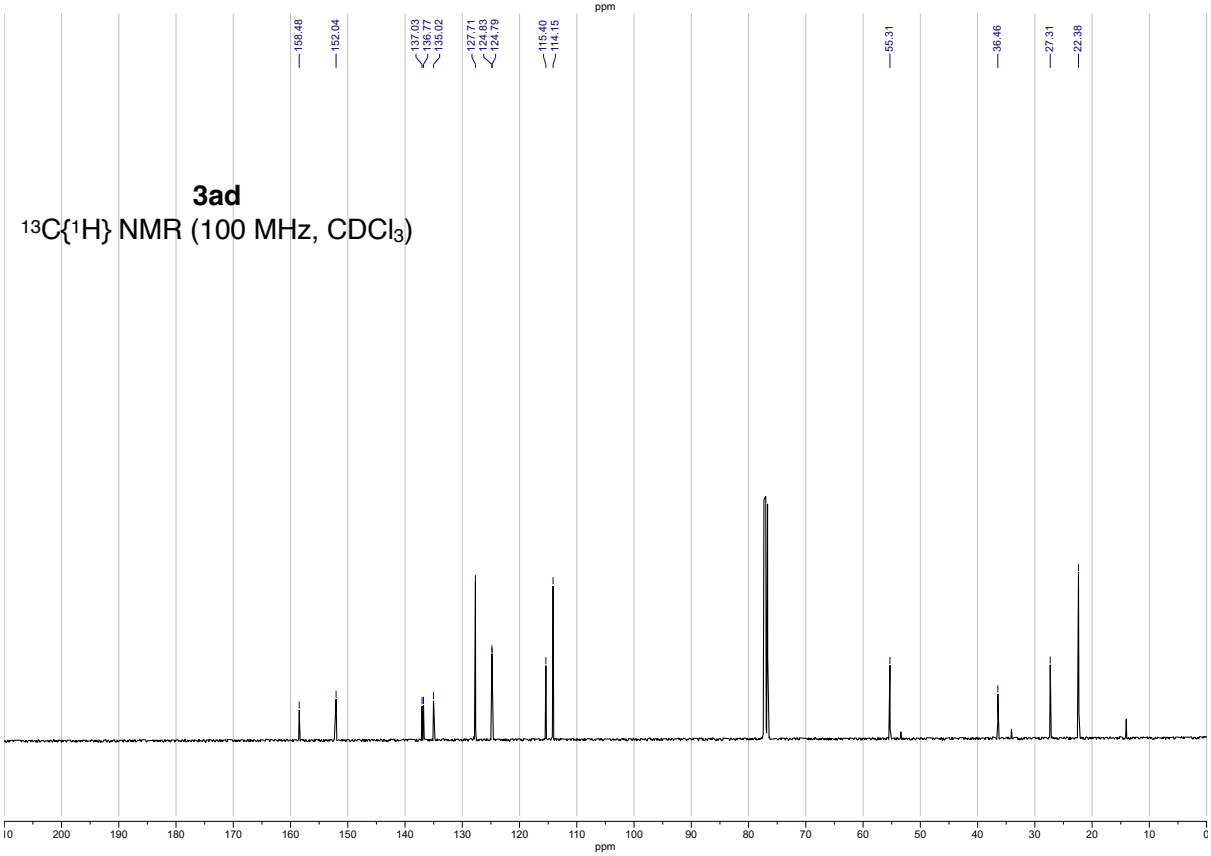
3ac

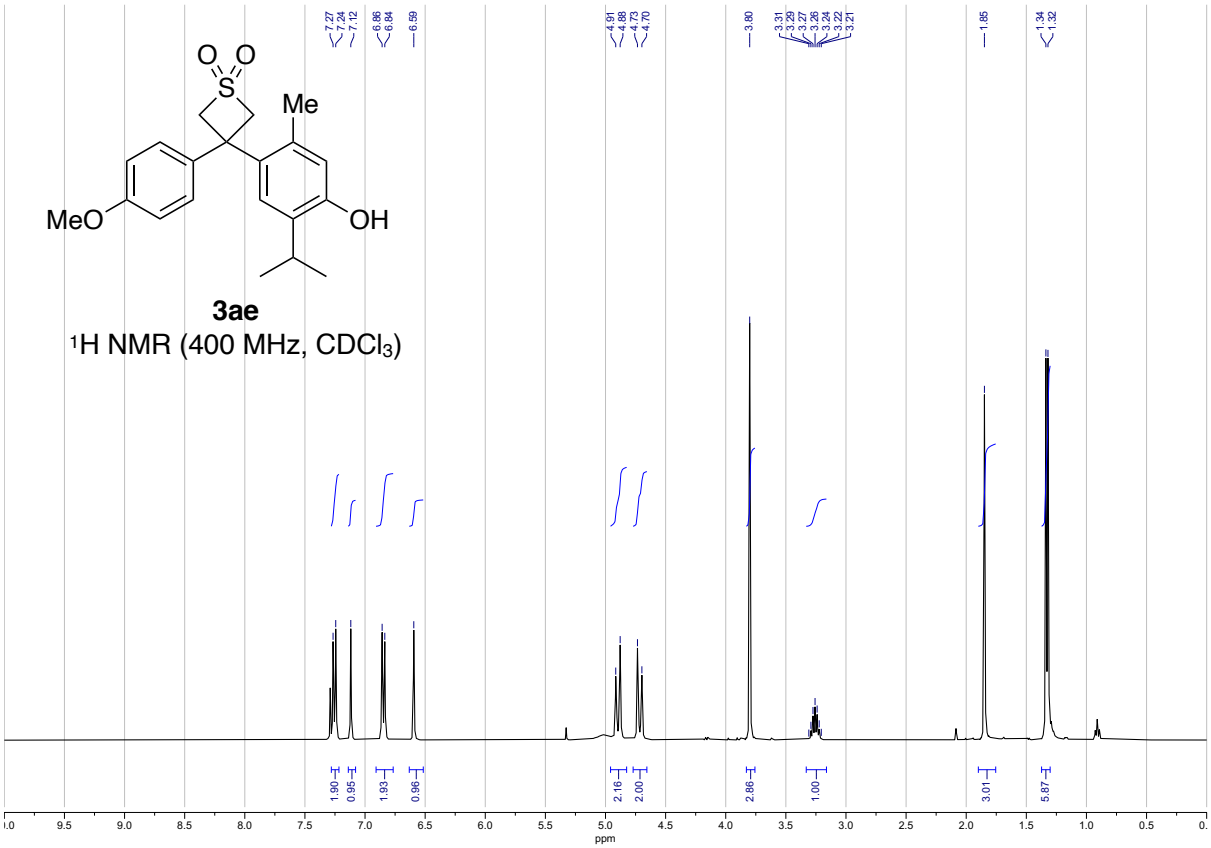
$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$)


O
O
S
Me
MeO
OH
Me
3ac
HSQC
ppm
f1 (ppm)


3ac
HMBC
ppm
f1 (ppm)

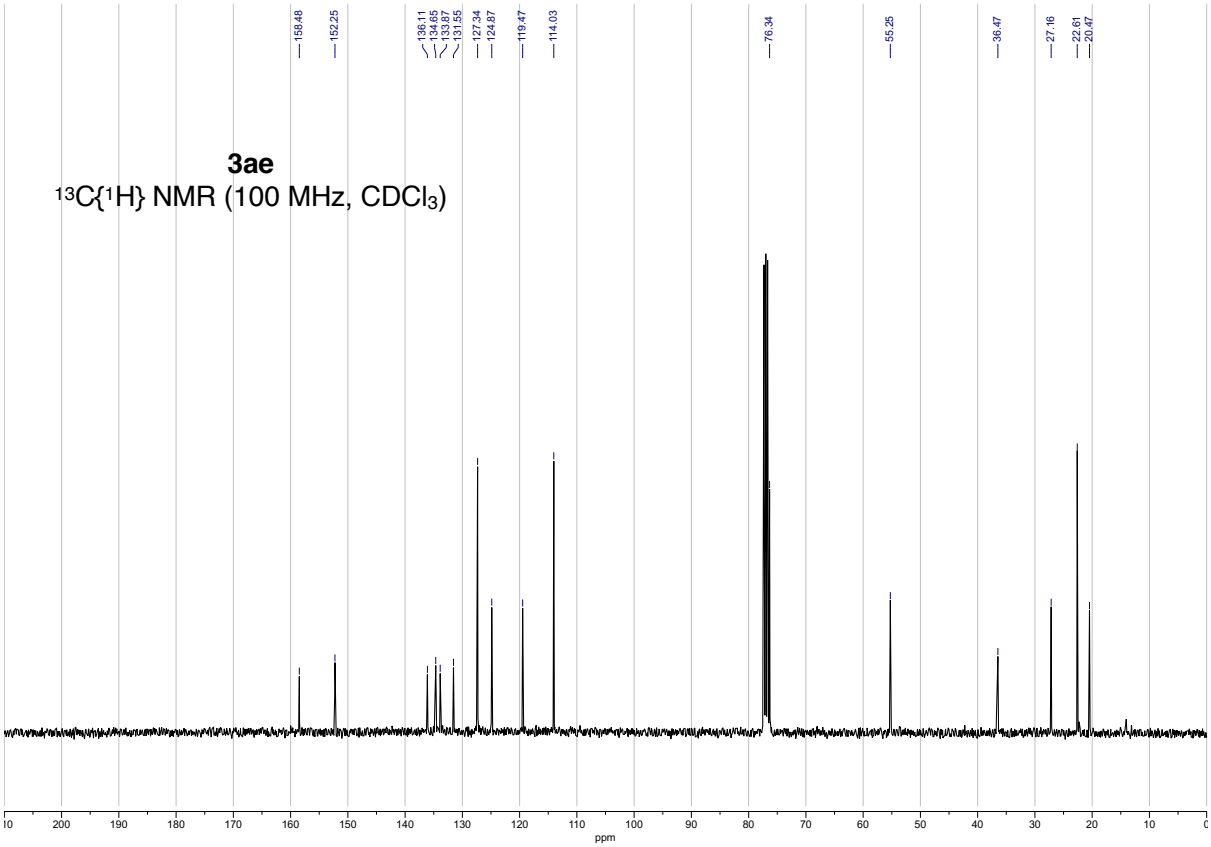

MeO
OH
3ad
1H NMR (400 MHz, CDCl3)
ppm


3ad
13C{1H} NMR (100 MHz, CDCl3)
ppm



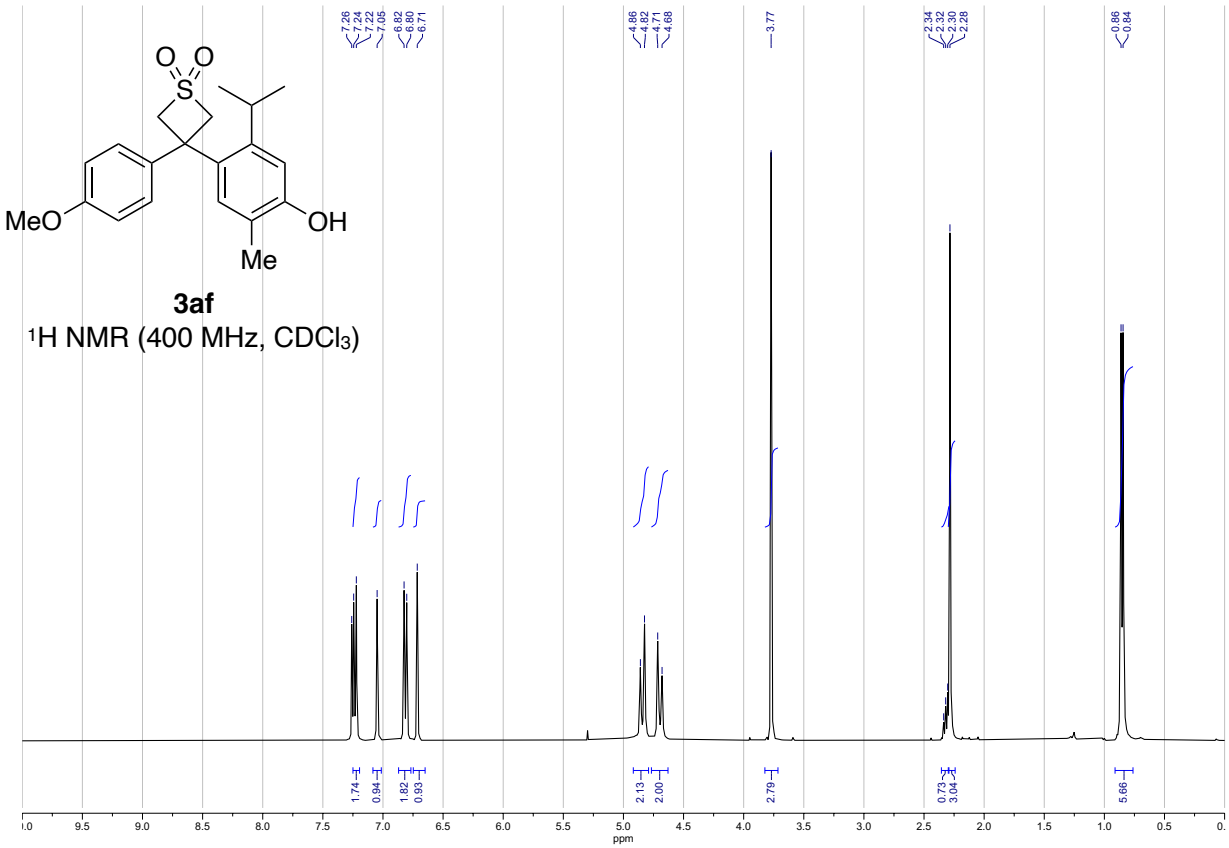
3ae

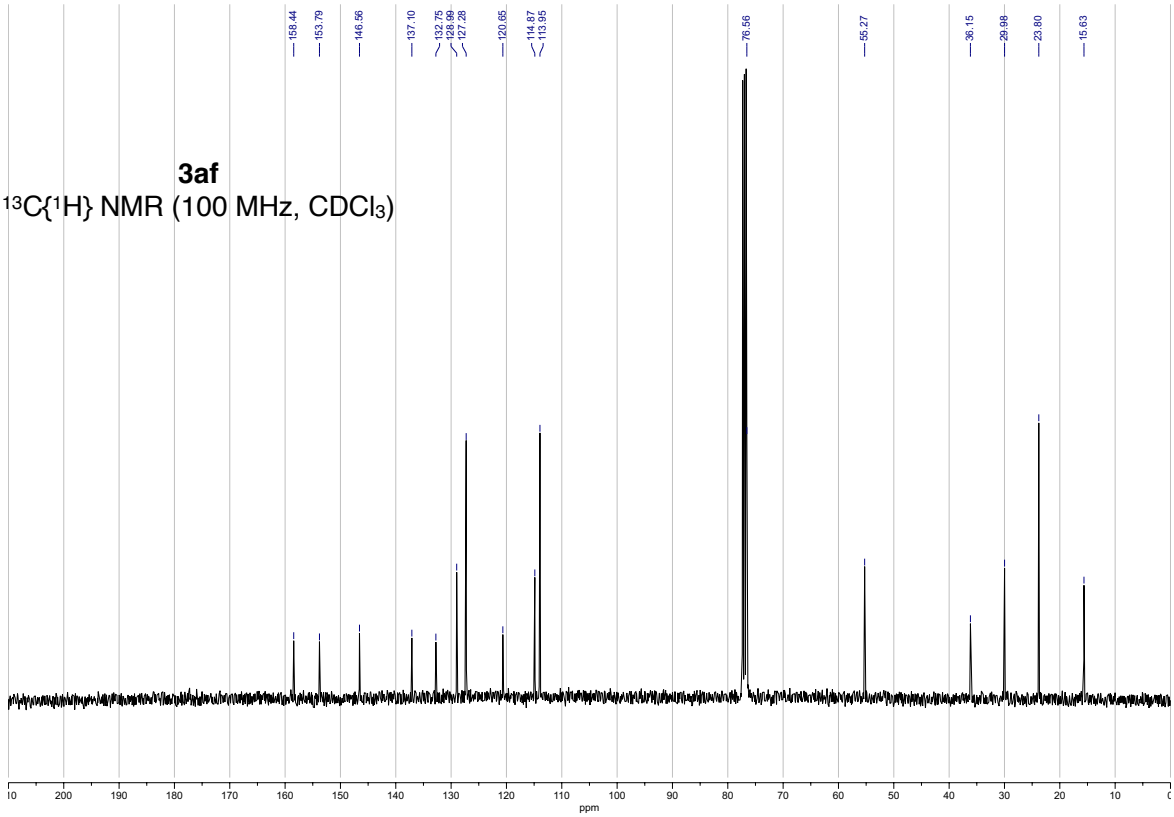
^{1}H NMR (400 MHz, $CDCl_3$)

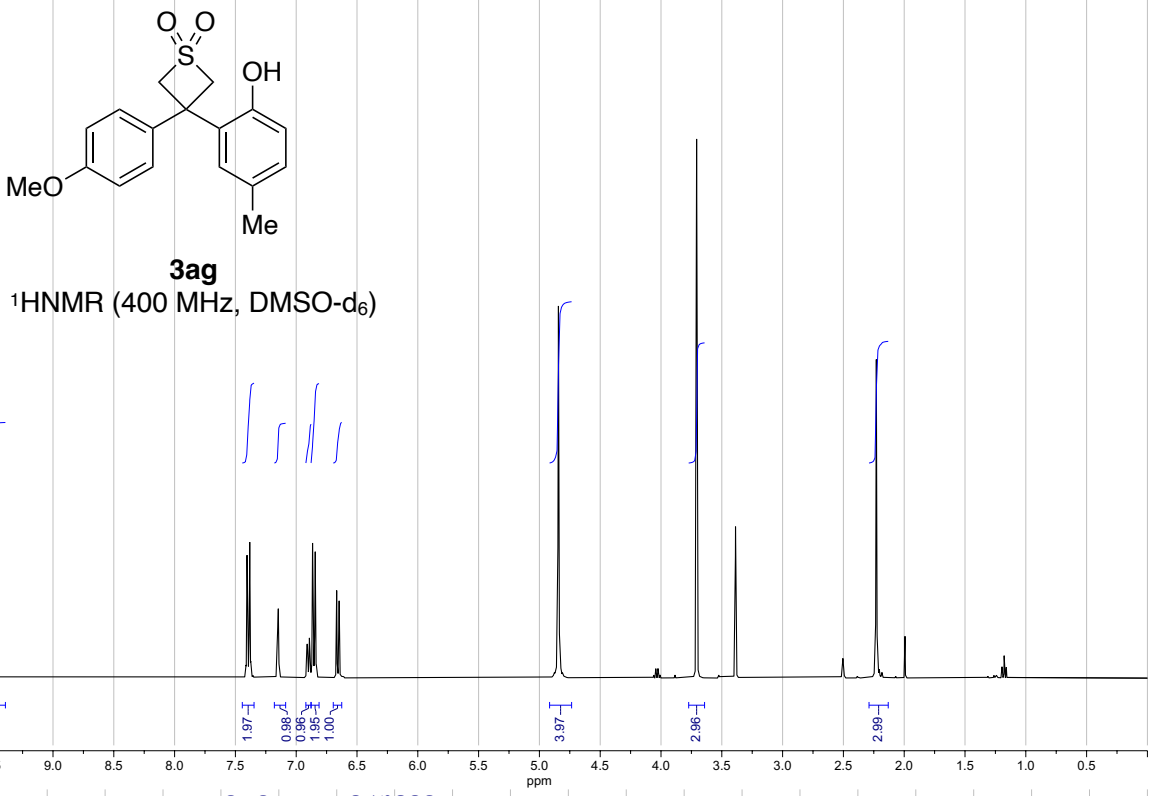


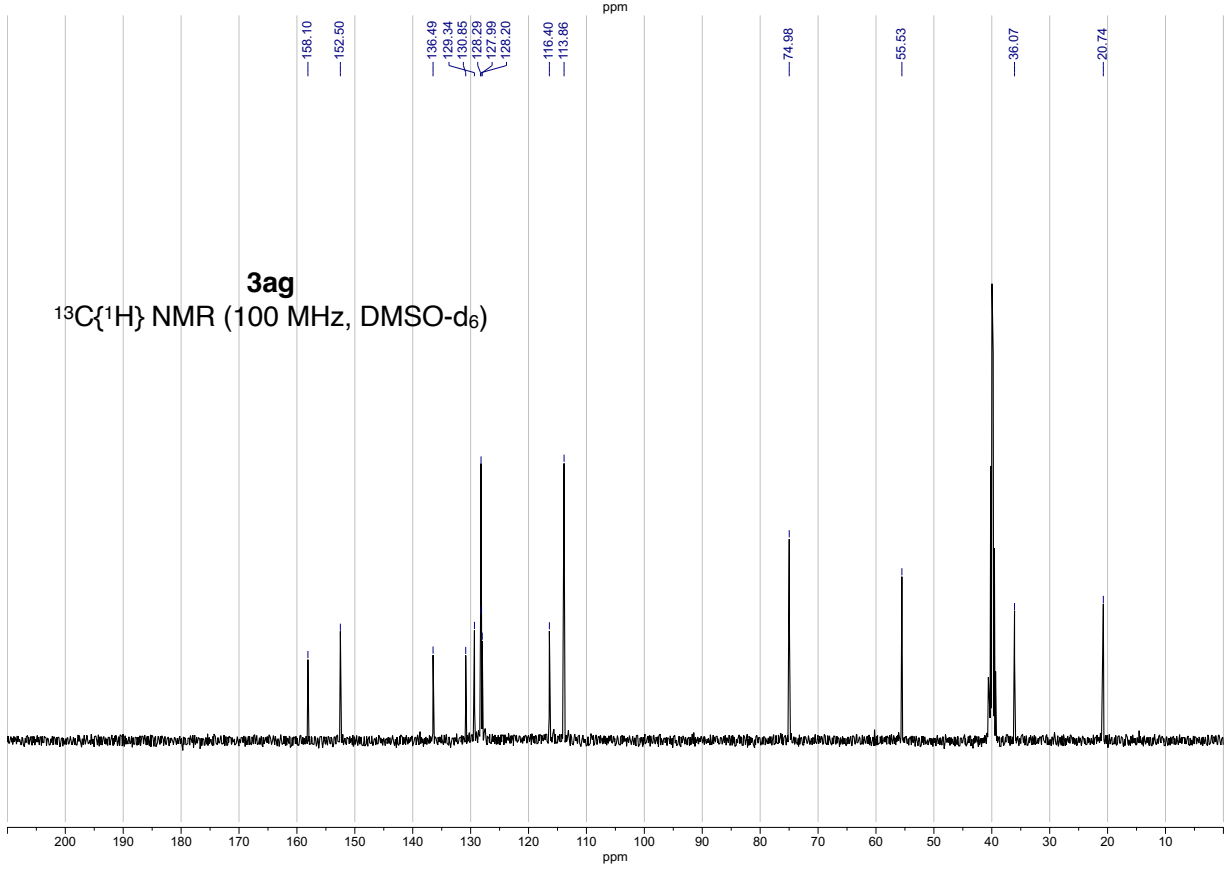
3ae

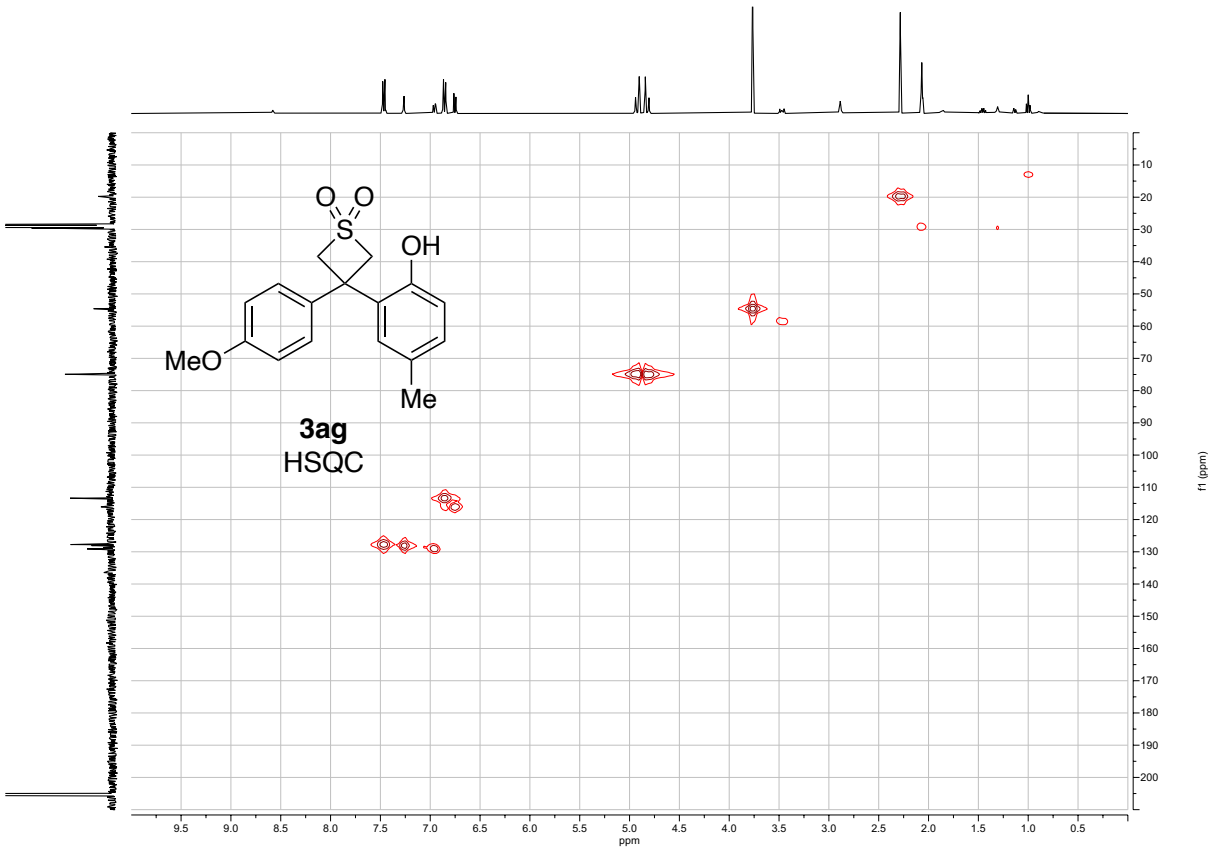
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)

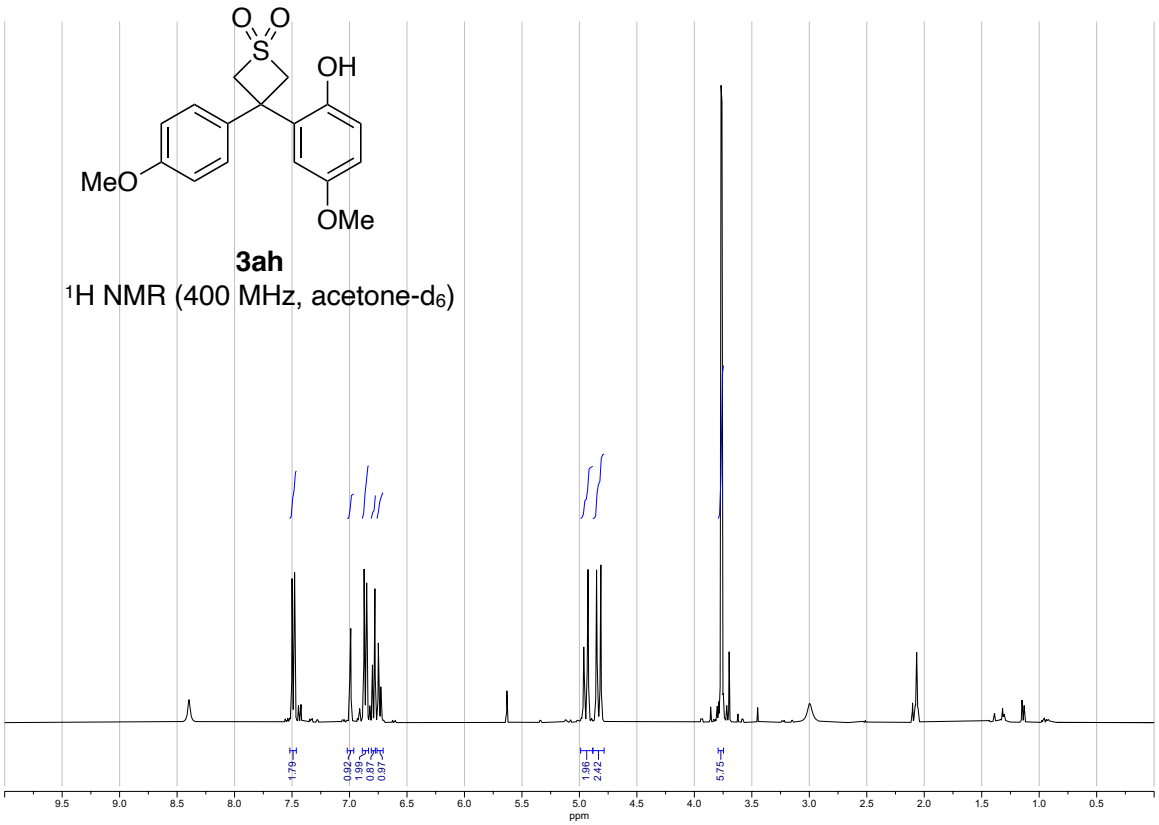

MeO
OH
Me
3af
^{1}H NMR (400 MHz, CDCl$_3$)
ppm

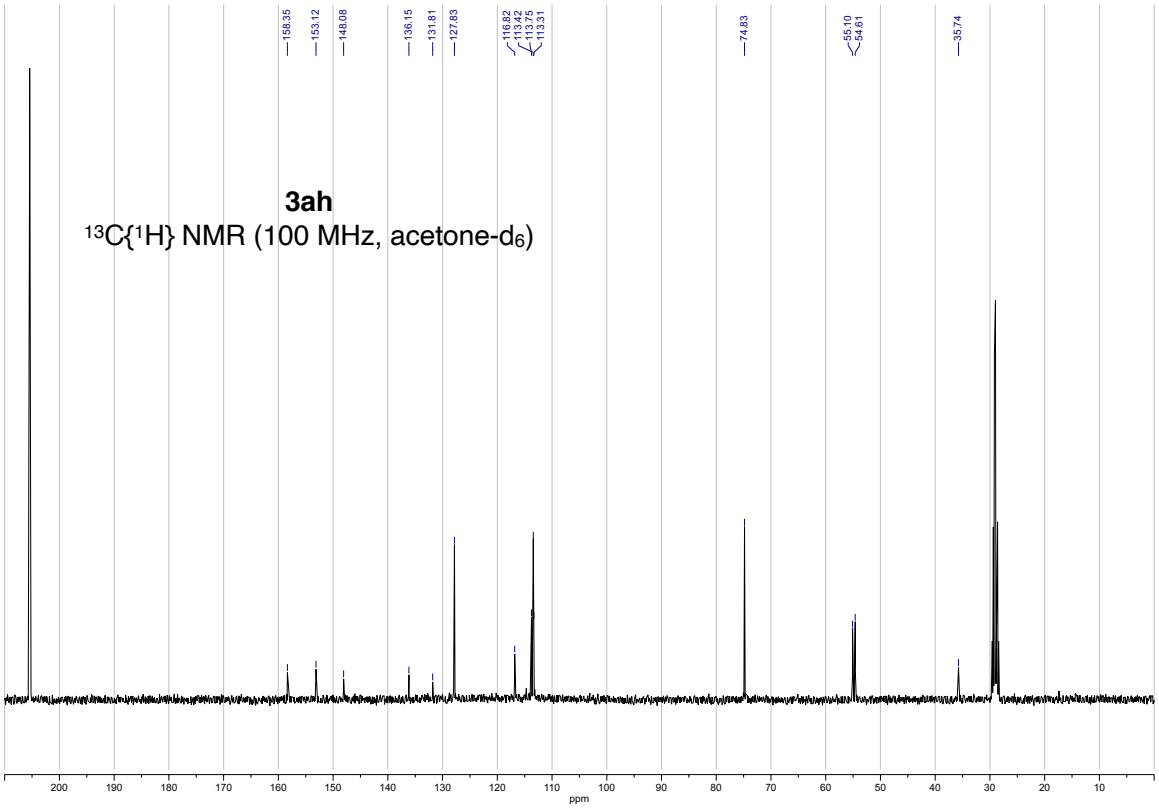

3af
^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$)
ppm

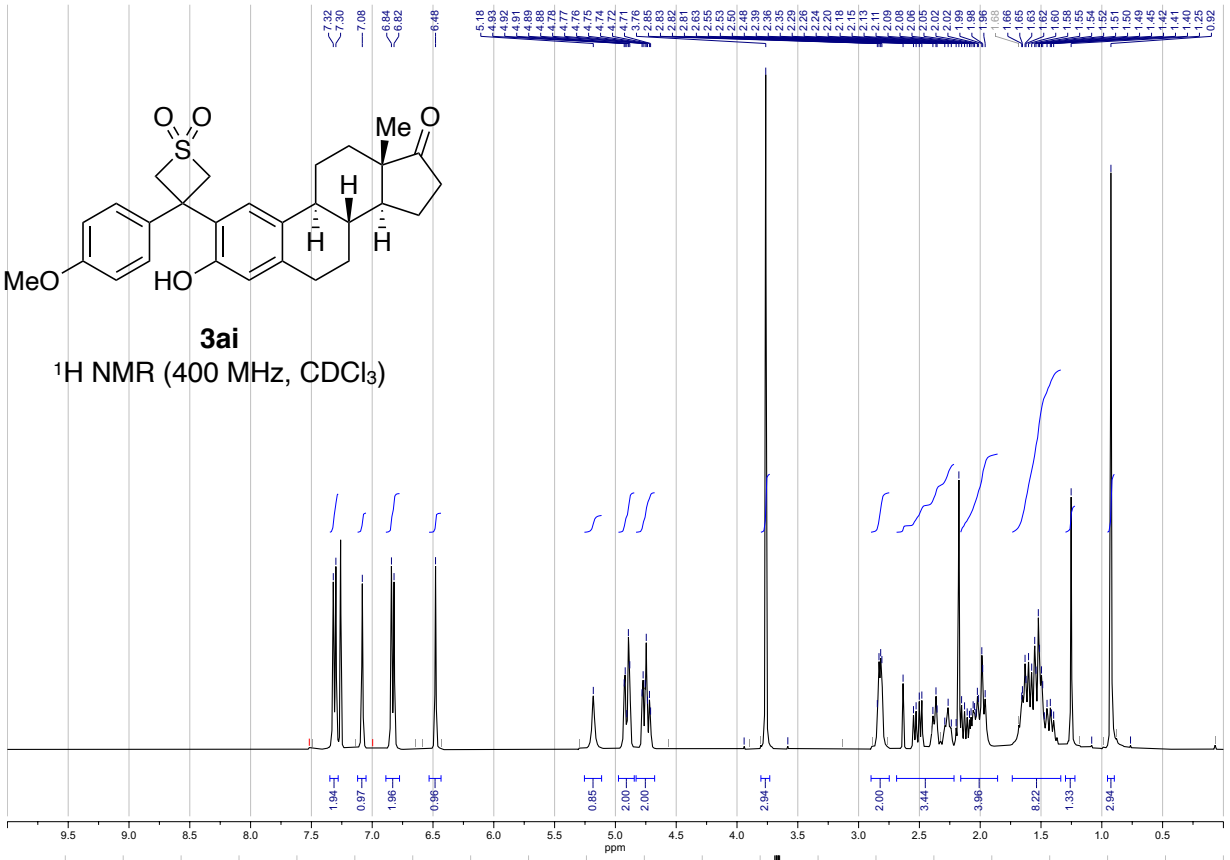

O
O
S
OH
MeO
Me
3ag
1HNMR (400 MHz, DMSO-d6)
1.00
1.97
0.98
0.96
1.95
1.00
3.97
2.96
2.99
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
ppm


158.10
152.50
136.49
129.34
130.85
128.29
127.99
128.20
116.40
113.86
74.98
55.53
36.07
20.74
3ag
13C{1H} NMR (100 MHz, DMSO-d6)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
ppm


O
O
S
OH
MeO
Me
3ag
HSQC
ppm
f1 (ppm)


O
O
S
OH
MeO
OMe
3ah
1H NMR (400 MHz, acetone-d6)
1.79
0.92
1.99
0.87
0.97
1.96
2.42
5.75
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
ppm


158.35
153.12
148.08
136.15
131.81
127.83
116.82
113.42
113.75
113.31
74.83
55.10
54.61
35.74
3ah
13C{1H} NMR (100 MHz, acetone-d6)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
ppm

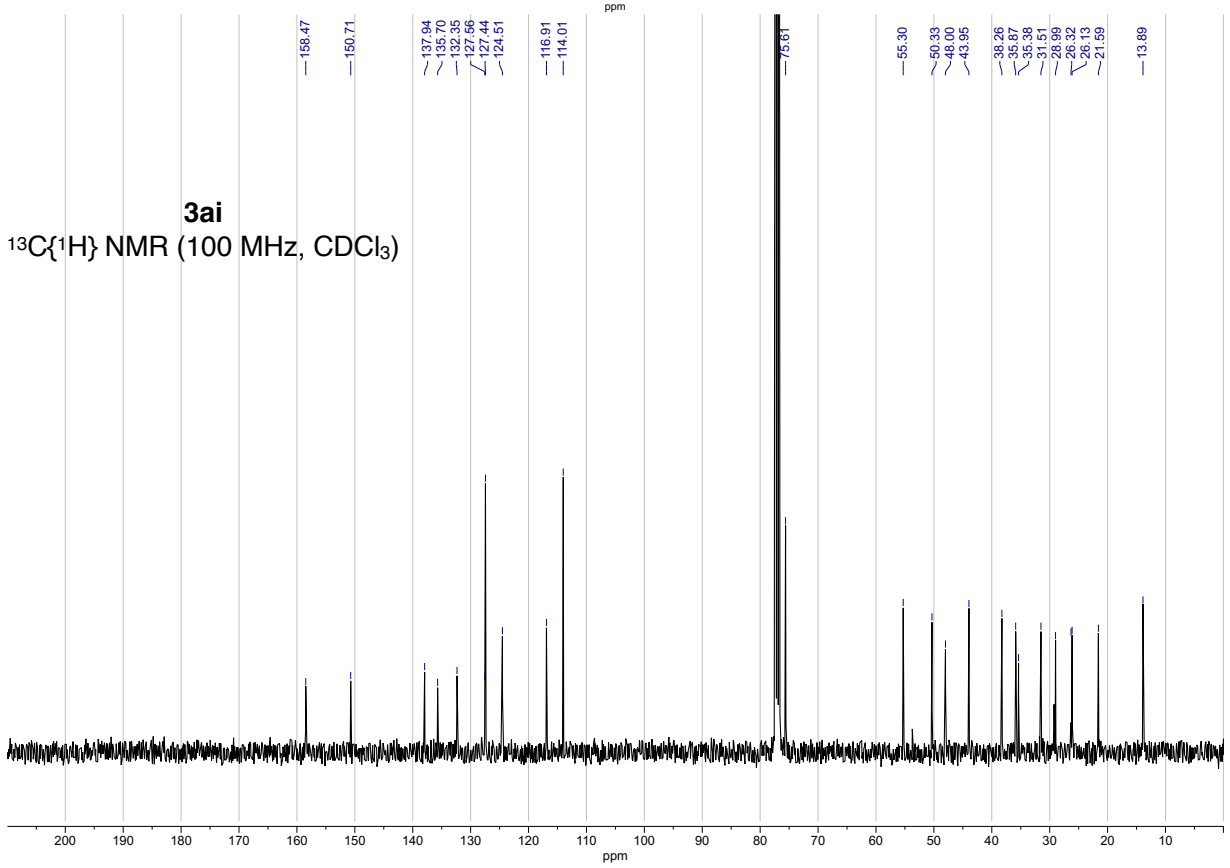


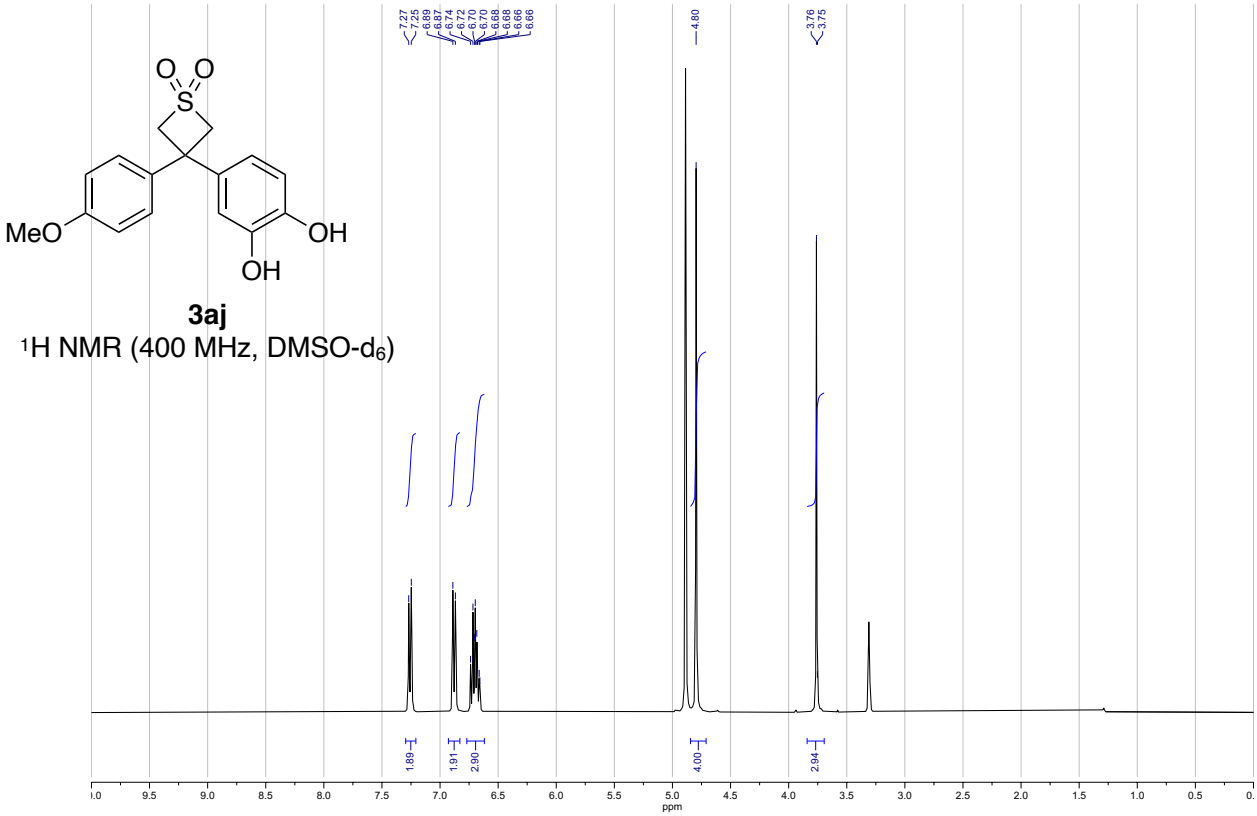
3ai

^{1}H NMR (400 MHz, $CDCl_3$)

3ai

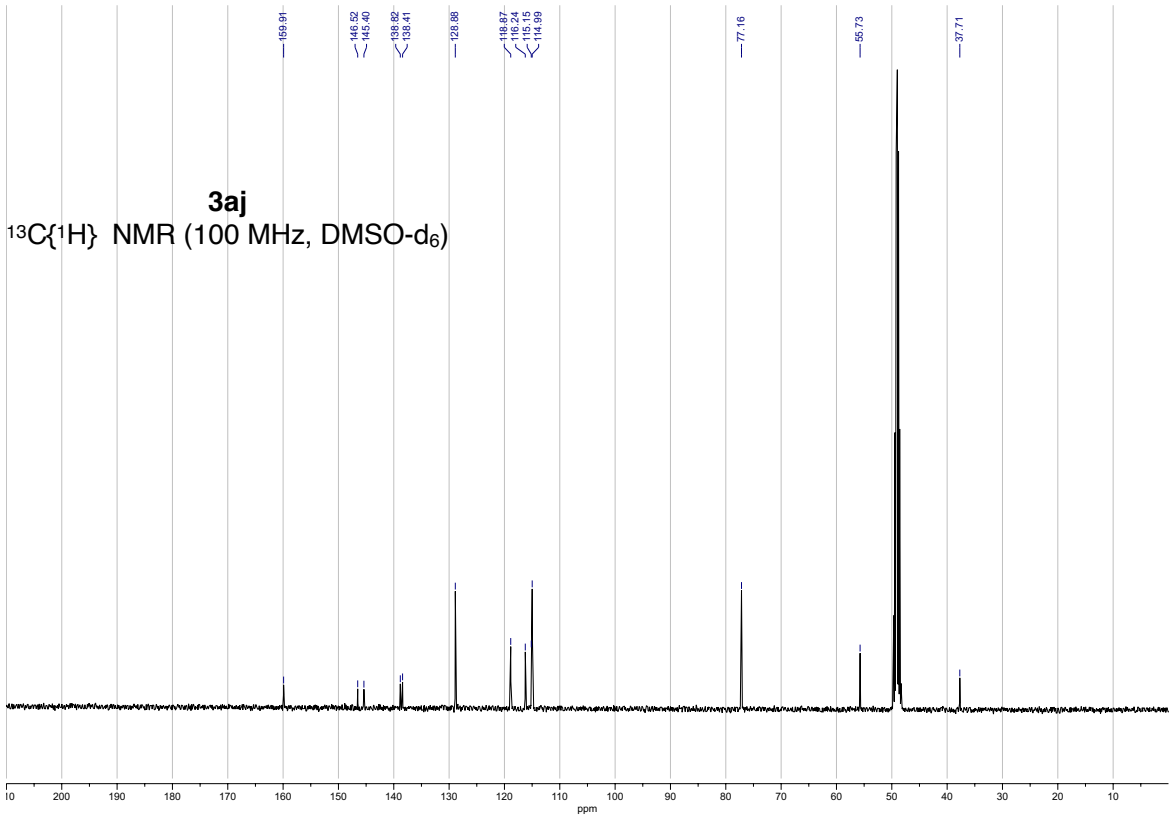
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)





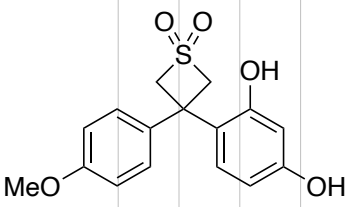
3aj

^{1}H NMR (400 MHz, DMSO-d$_6$)



3aj

^{13}C{^{1}H} NMR (100 MHz, DMSO-d$_6$)

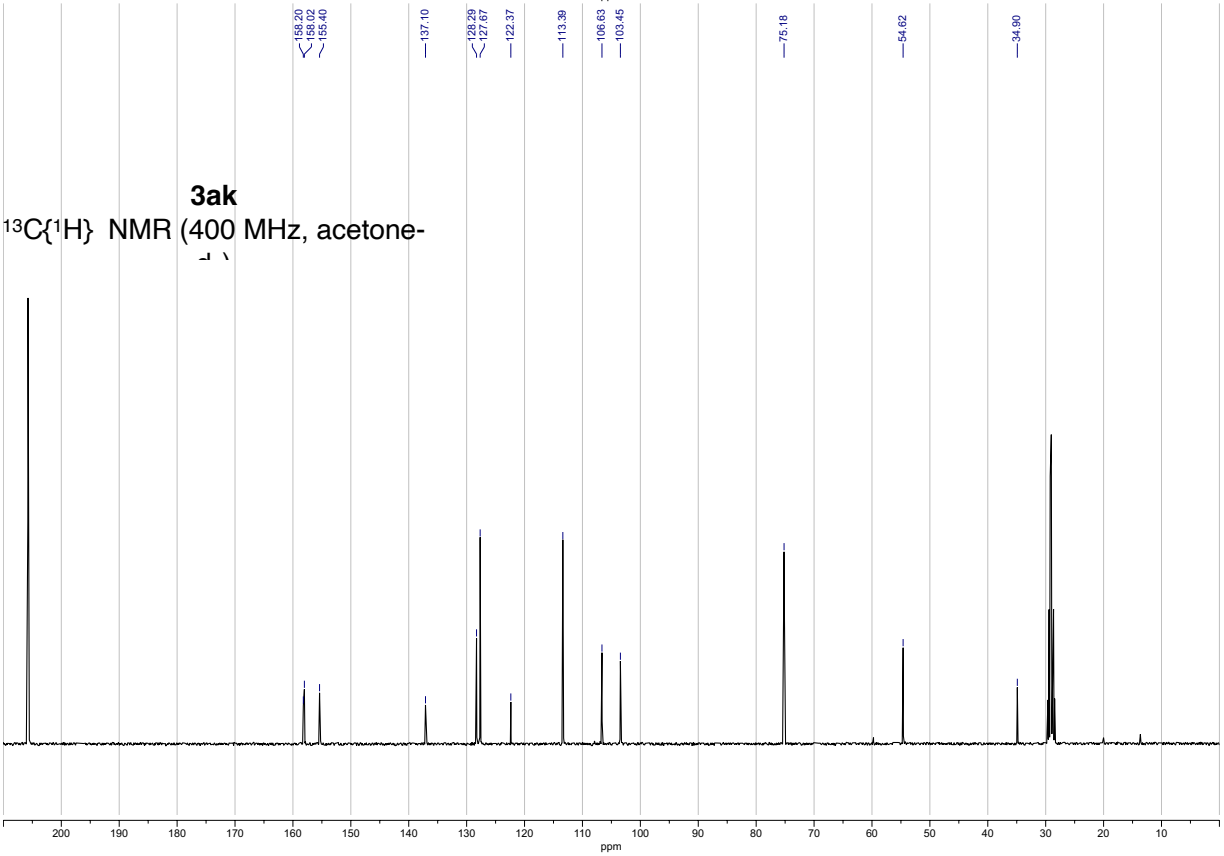


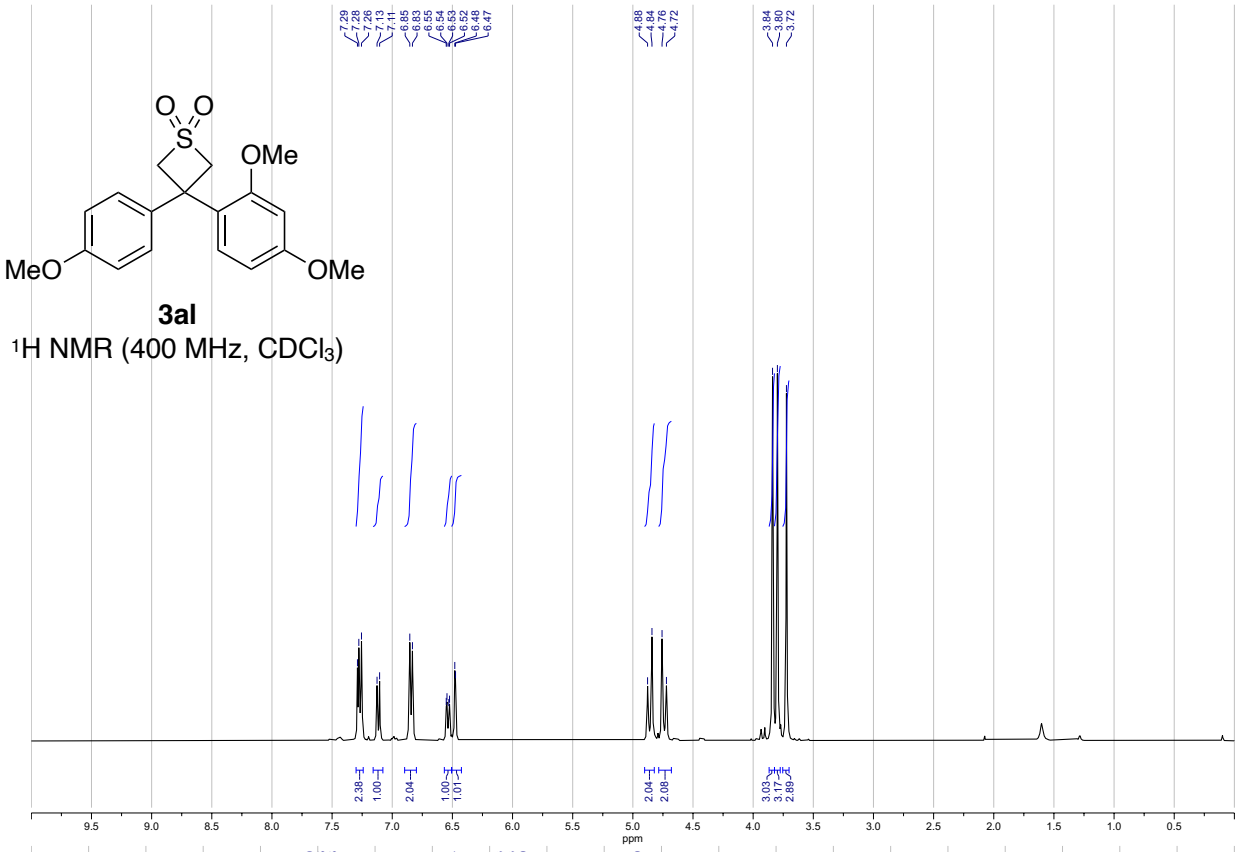
3ak

^{1}H NMR (400 MHz, acetone-d_6)

3ak

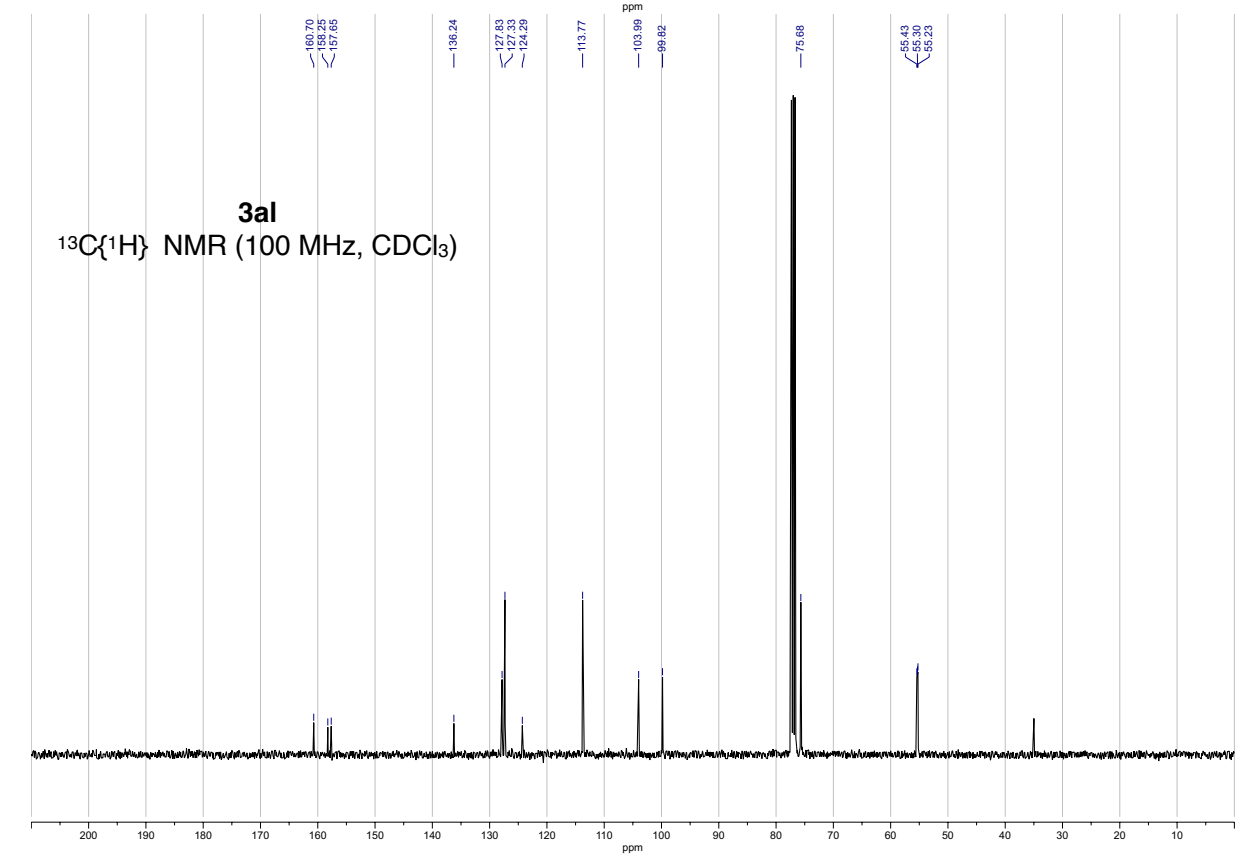
^{13}C{^{1}H} NMR (400 MHz, acetone-





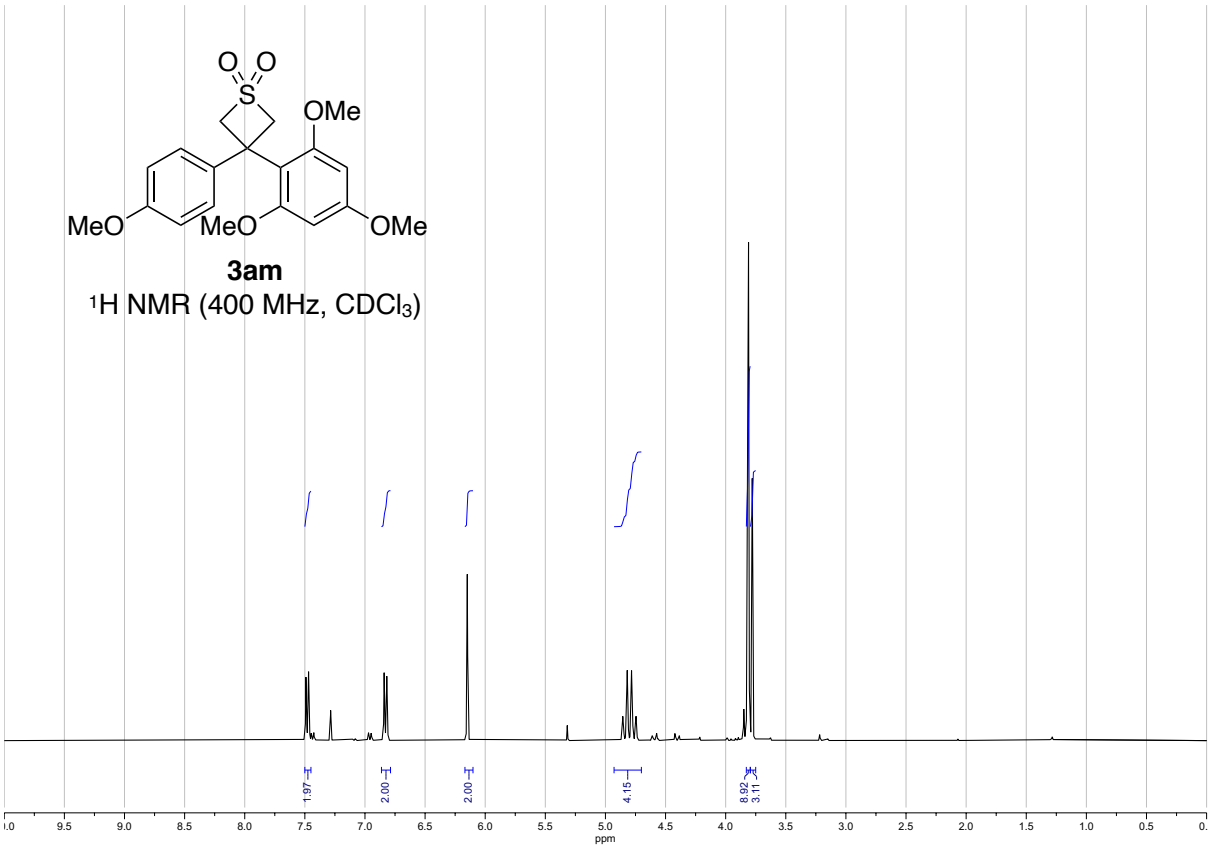
3al

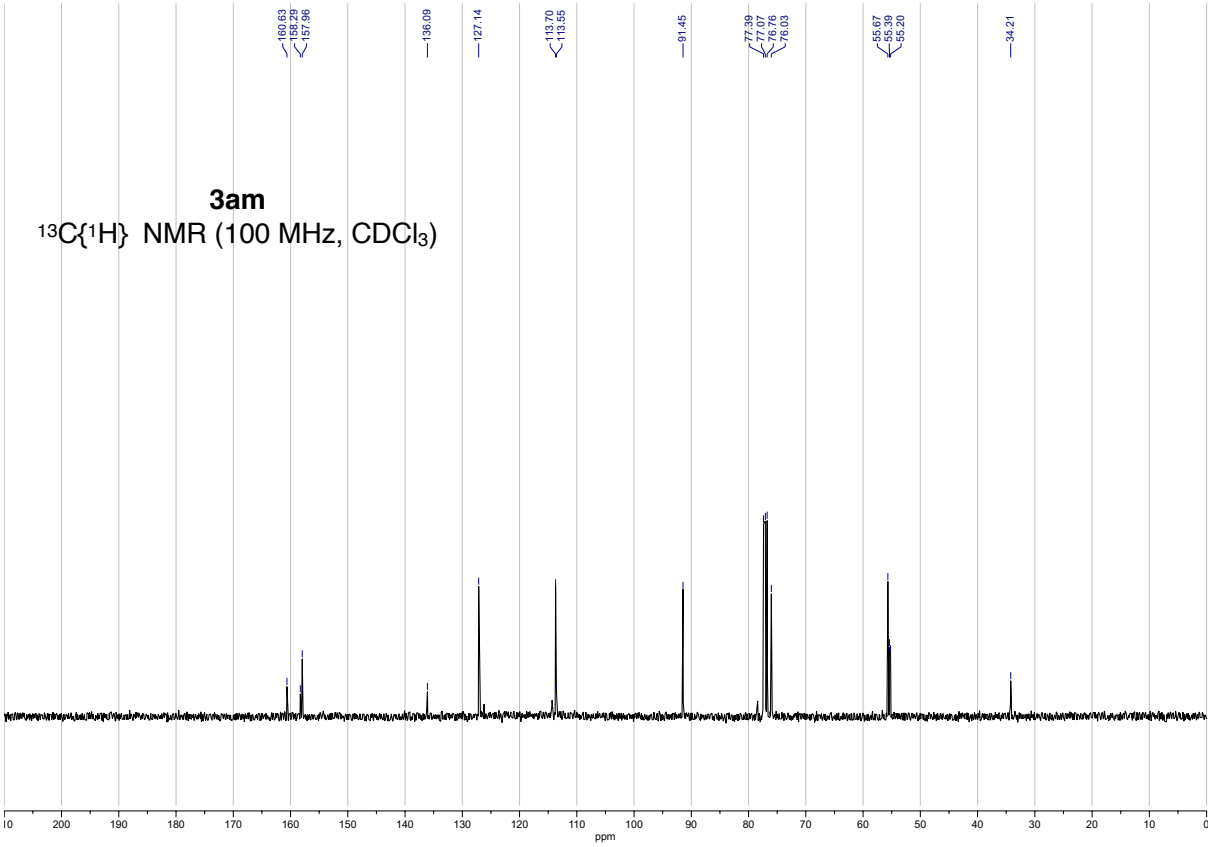
^{1}H NMR (400 MHz, $CDCl_3$)

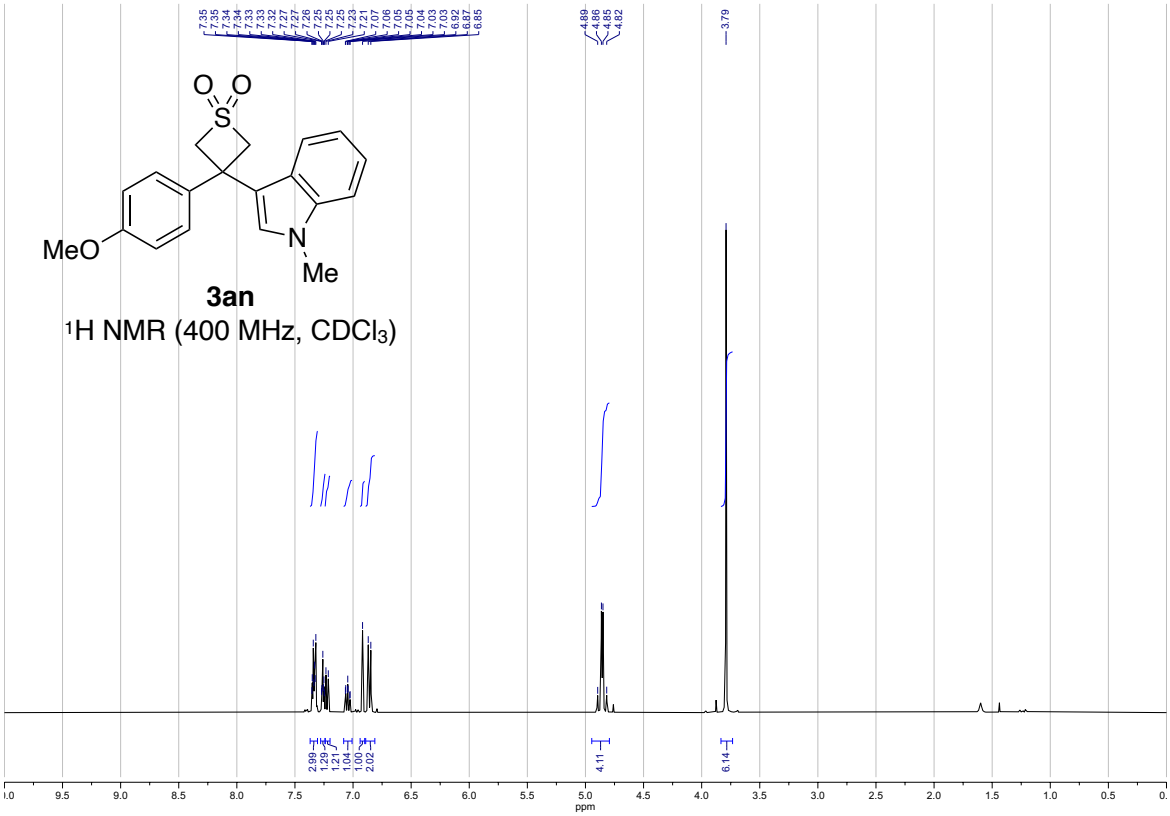


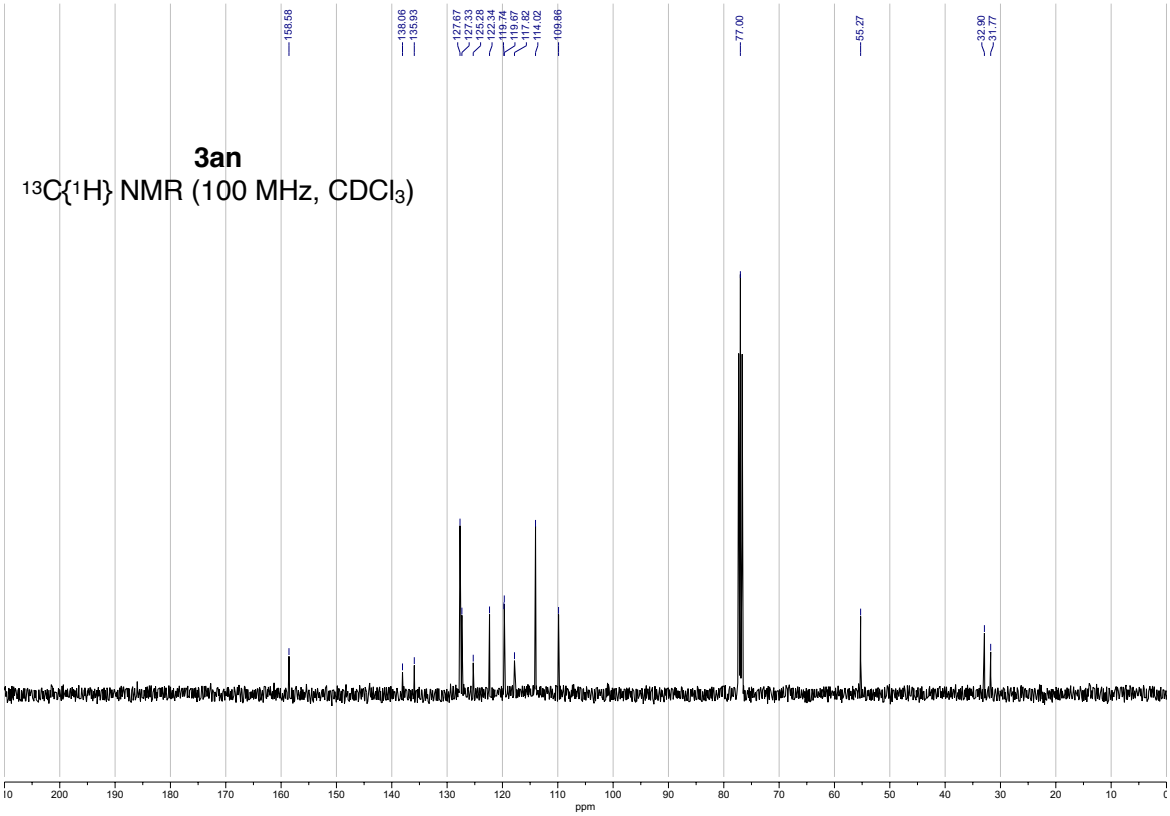
3al

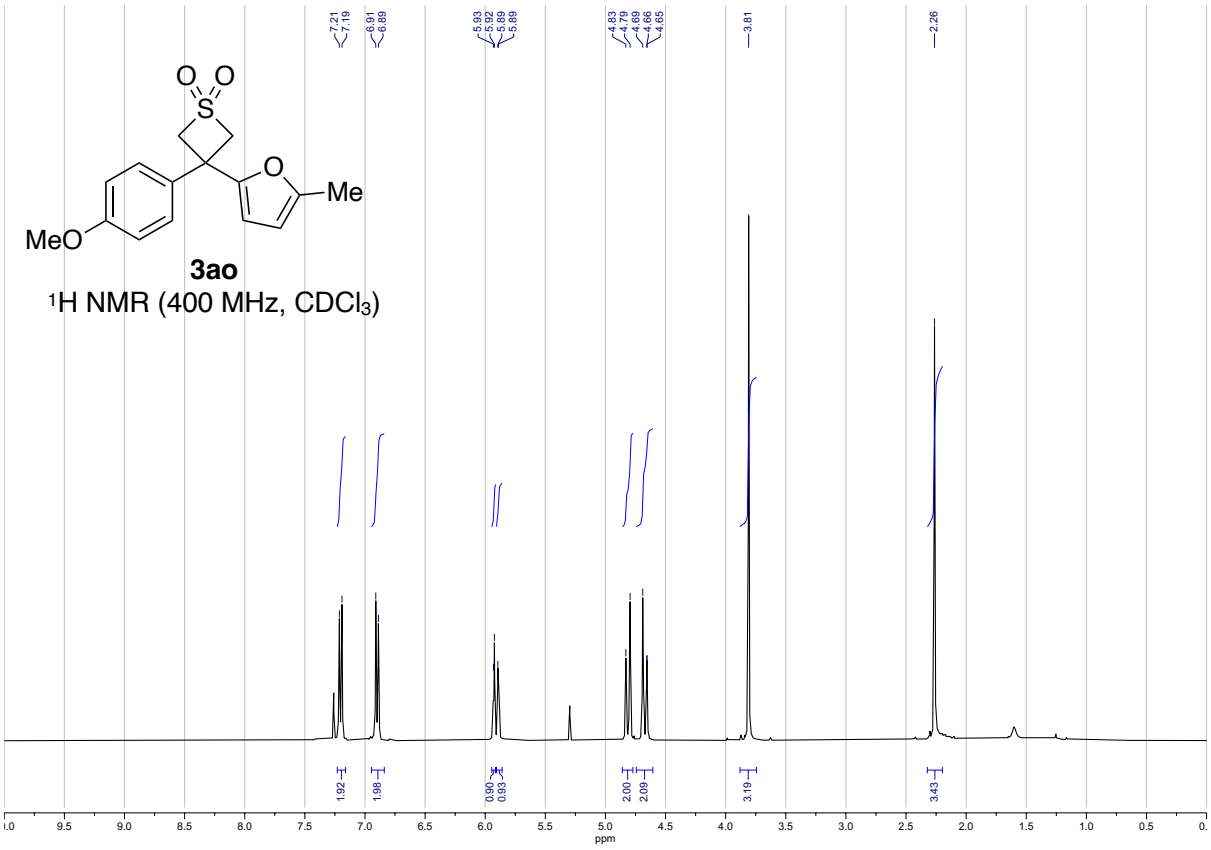
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)


O
O
S
OMe
MeO
MeO
OMe
3am
1H NMR (400 MHz, CDCl3)
1.97
2.00
2.00
4.15
8.92
3.11
ppm


160.63
159.39
157.66
136.09
127.14
113.70
113.55
91.45
77.39
77.07
76.76
76.03
55.67
55.39
55.20
34.21
3am
13C{1H} NMR (100 MHz, CDCl3)
ppm

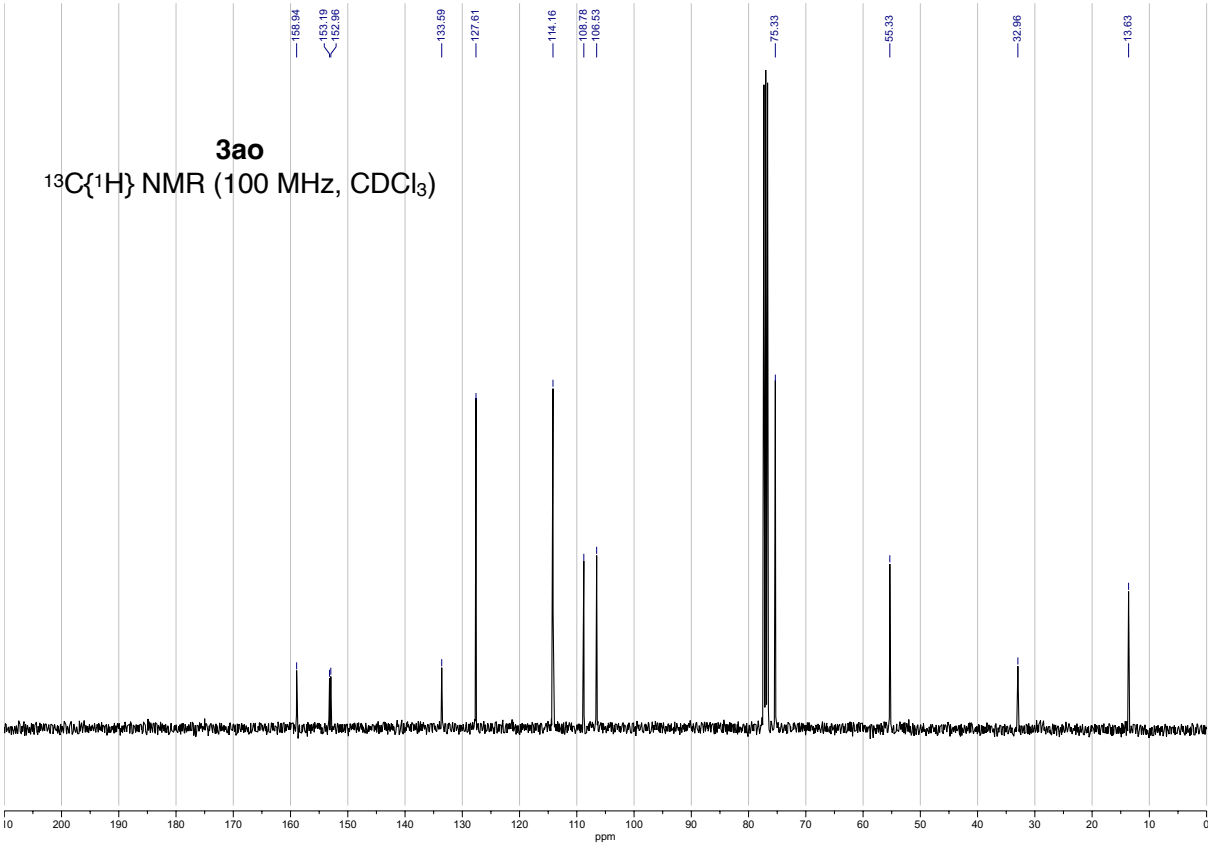

MeO
N
Me
3an
^{1}H NMR (400 MHz, CDCl$_3$)
ppm


3an
^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$)
ppm



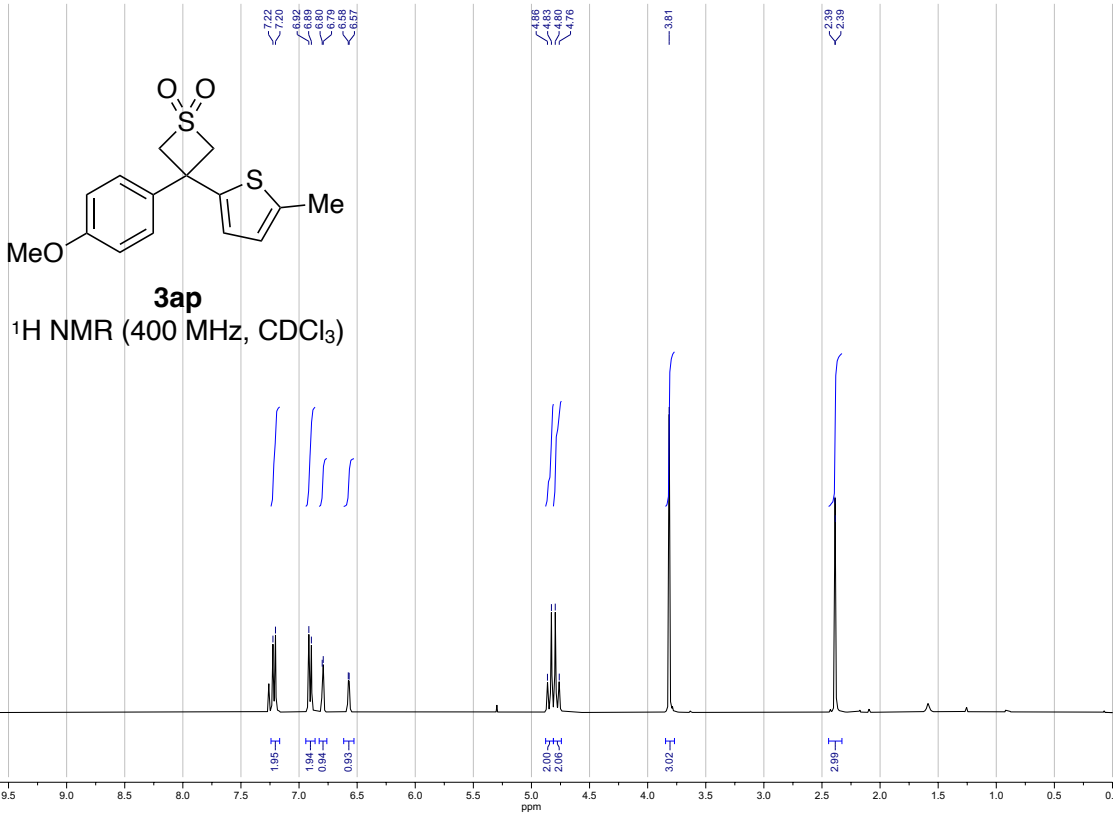
3ao

^{1}H NMR (400 MHz, $CDCl_3$)



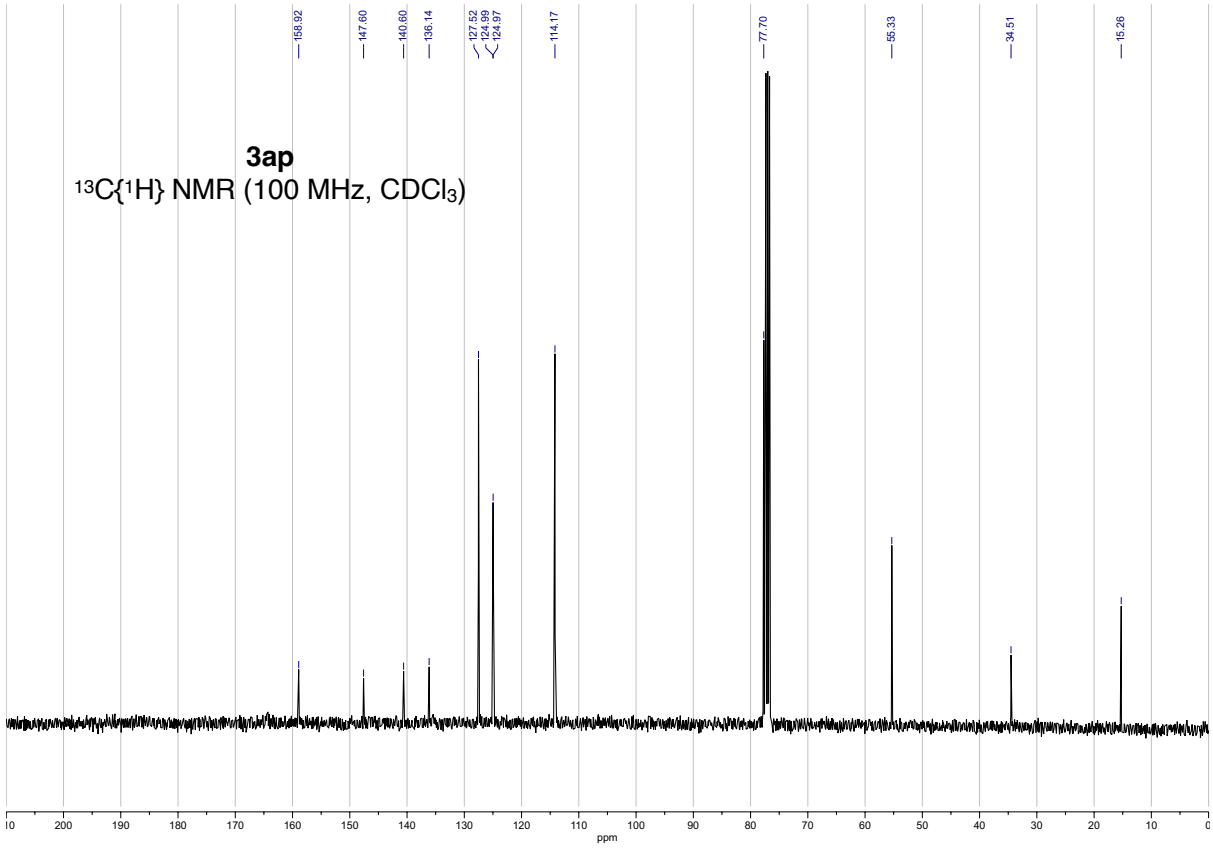
3ao

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)



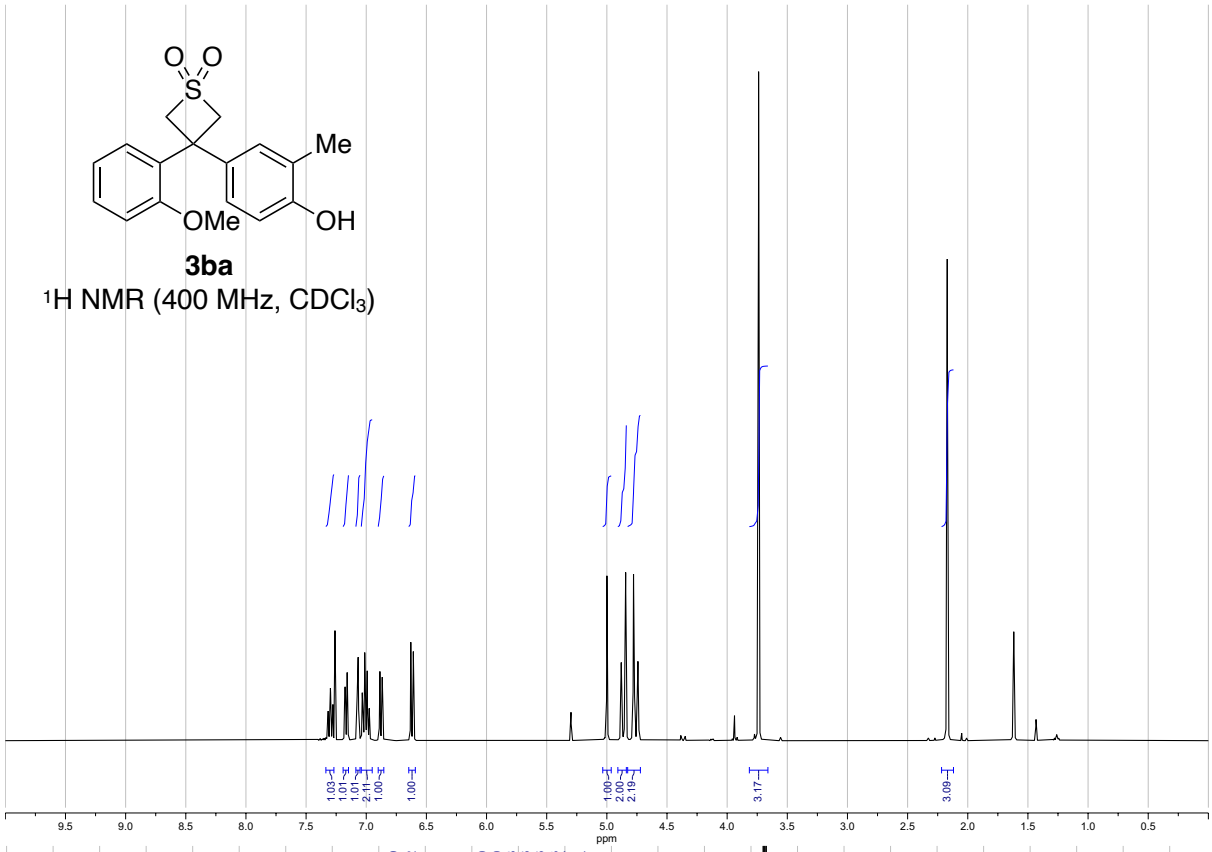
3ap

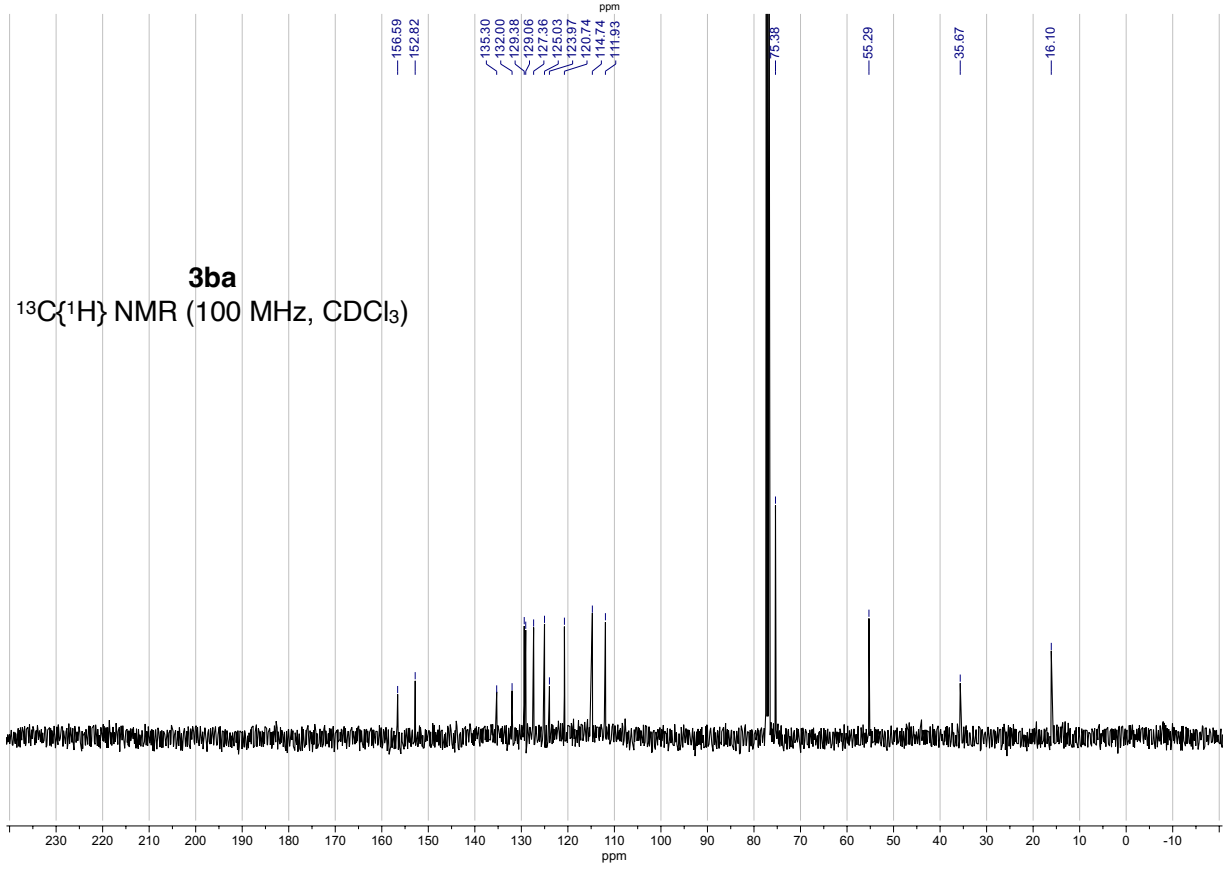
^{1}H NMR (400 MHz, $CDCl_3$)

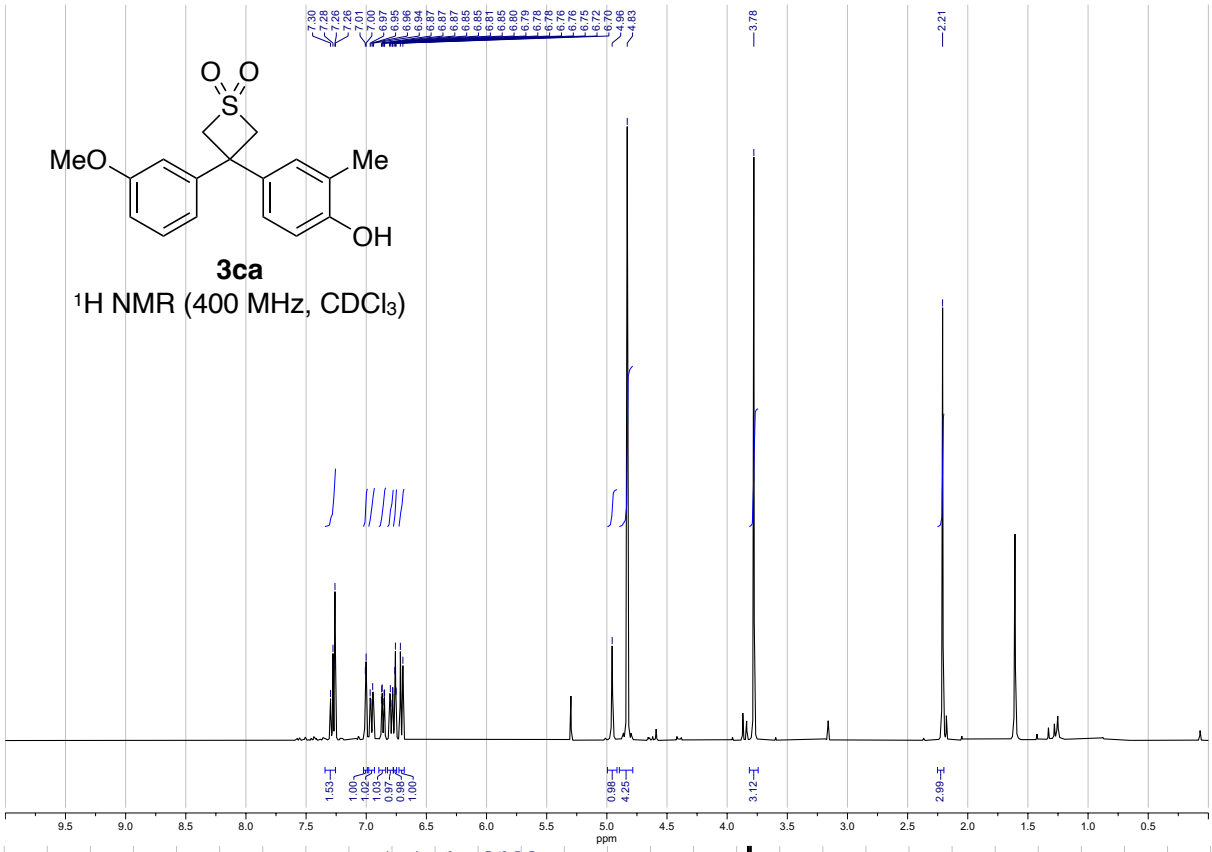


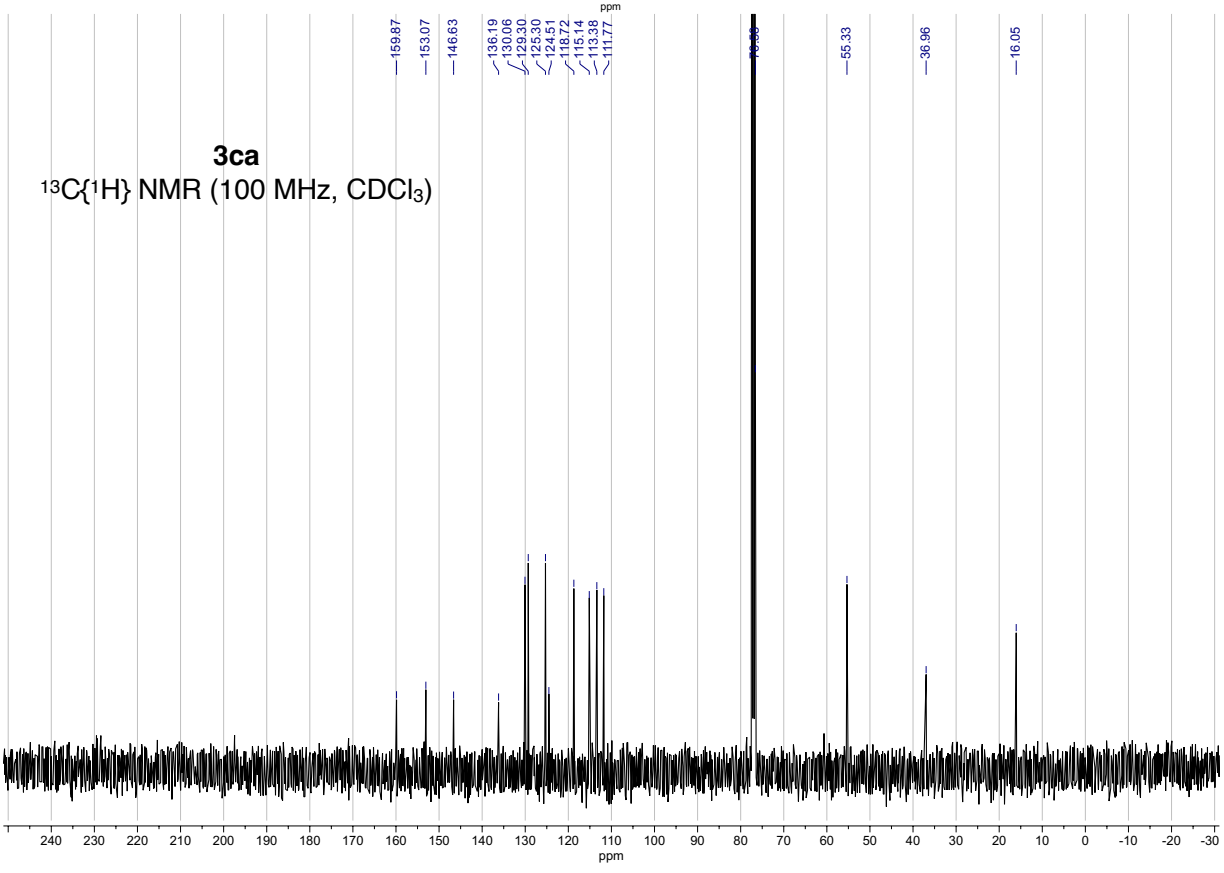
3ap

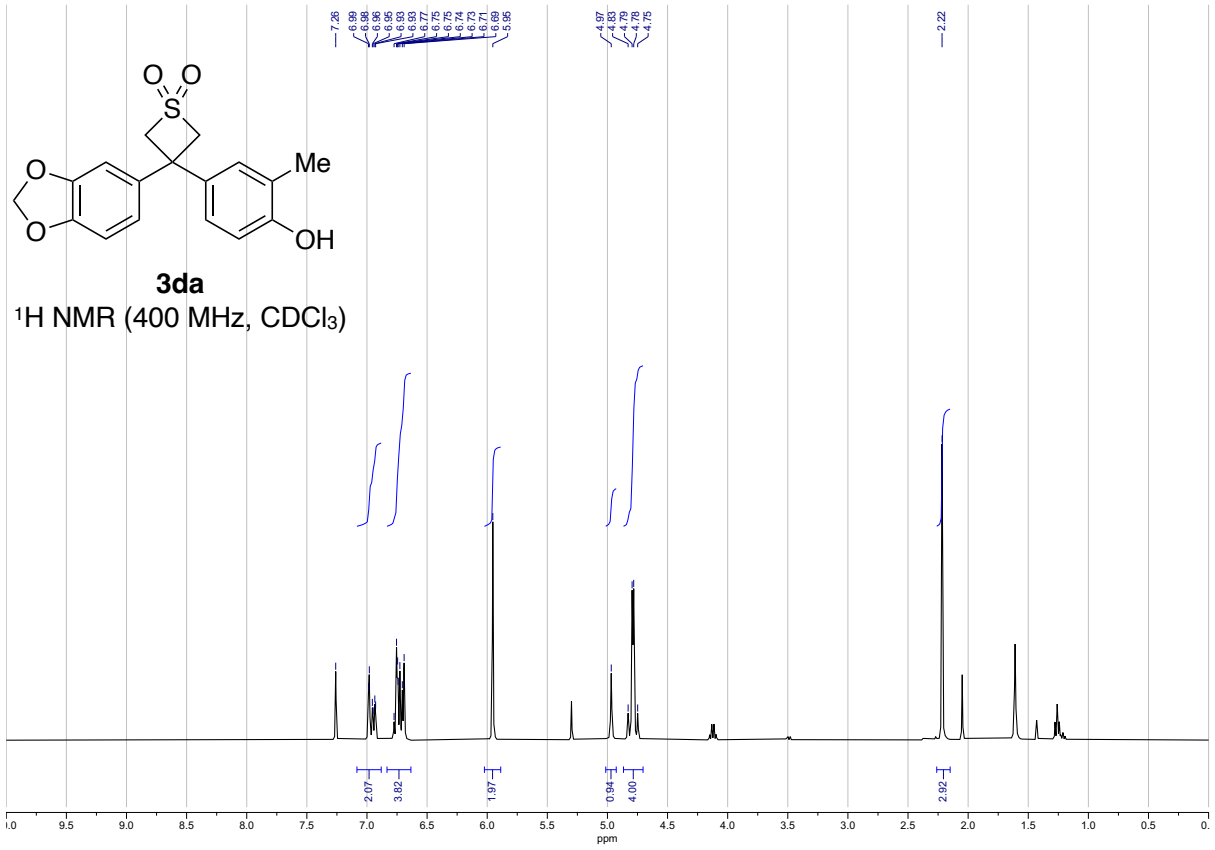
$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$)

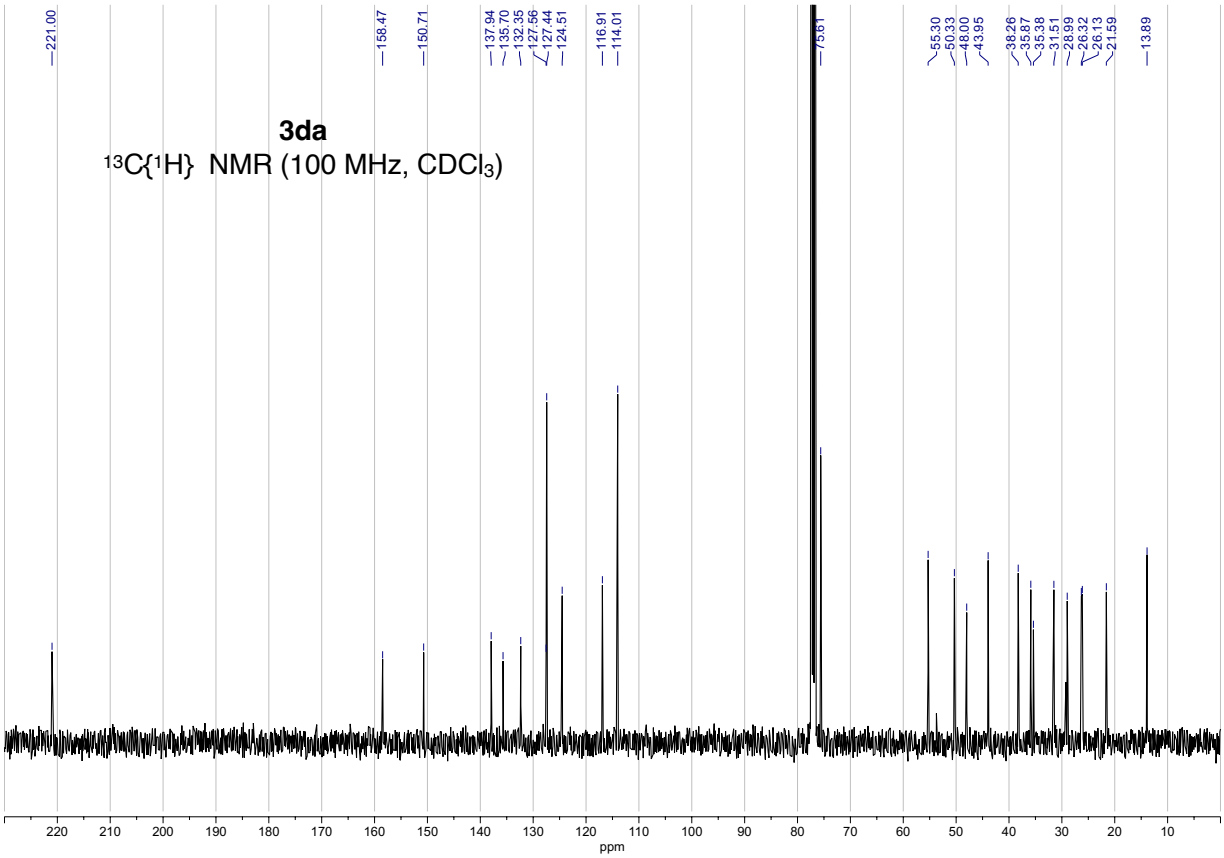

O
O
S
Me
OMe
OH
3ba
^{1}H NMR (400 MHz, CDCl$_3$)
1.03
1.01
1.01
2.01
1.00
1.00
1.00
2.00
2.19
3.17
3.09
ppm

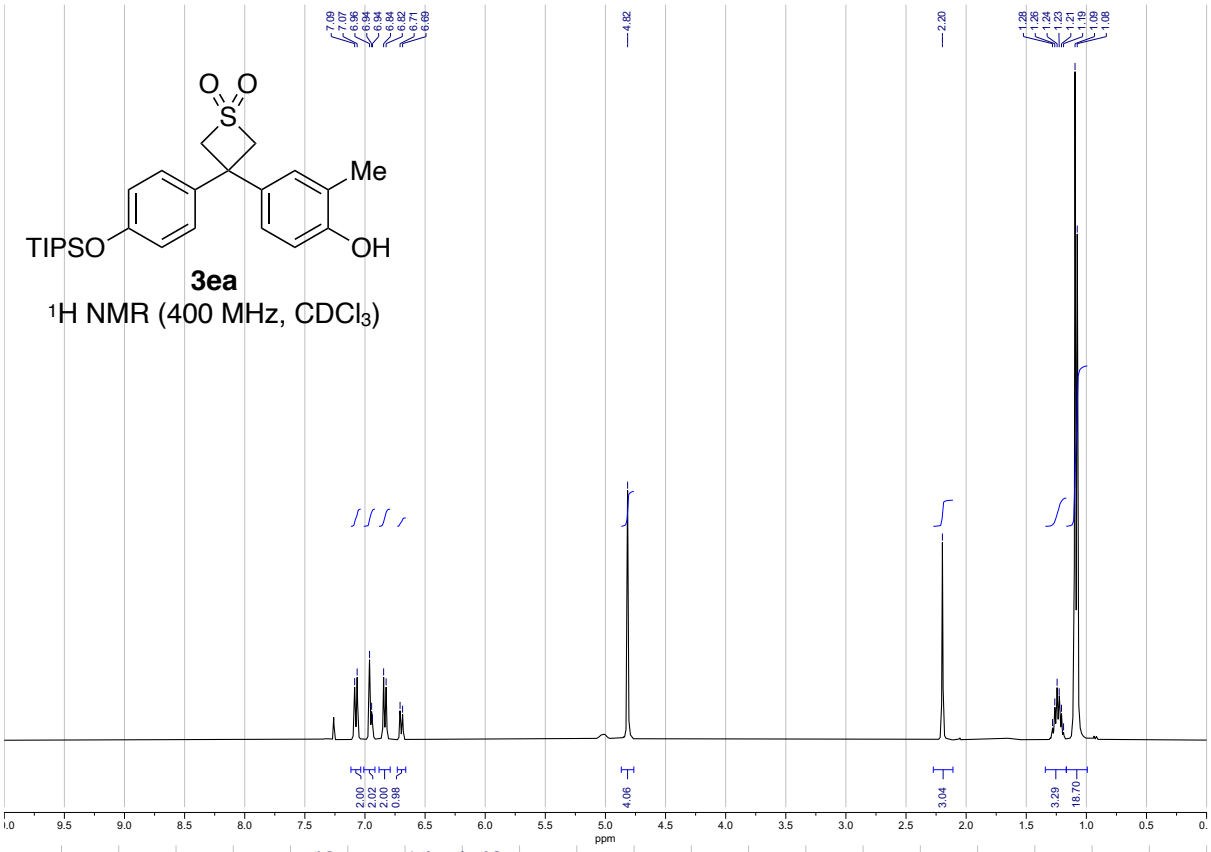

156.59
152.82
135.30
132.00
129.38
129.06
127.36
125.03
123.97
120.74
114.74
111.93
75.38
55.29
35.67
16.10
3ba
^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$)
ppm

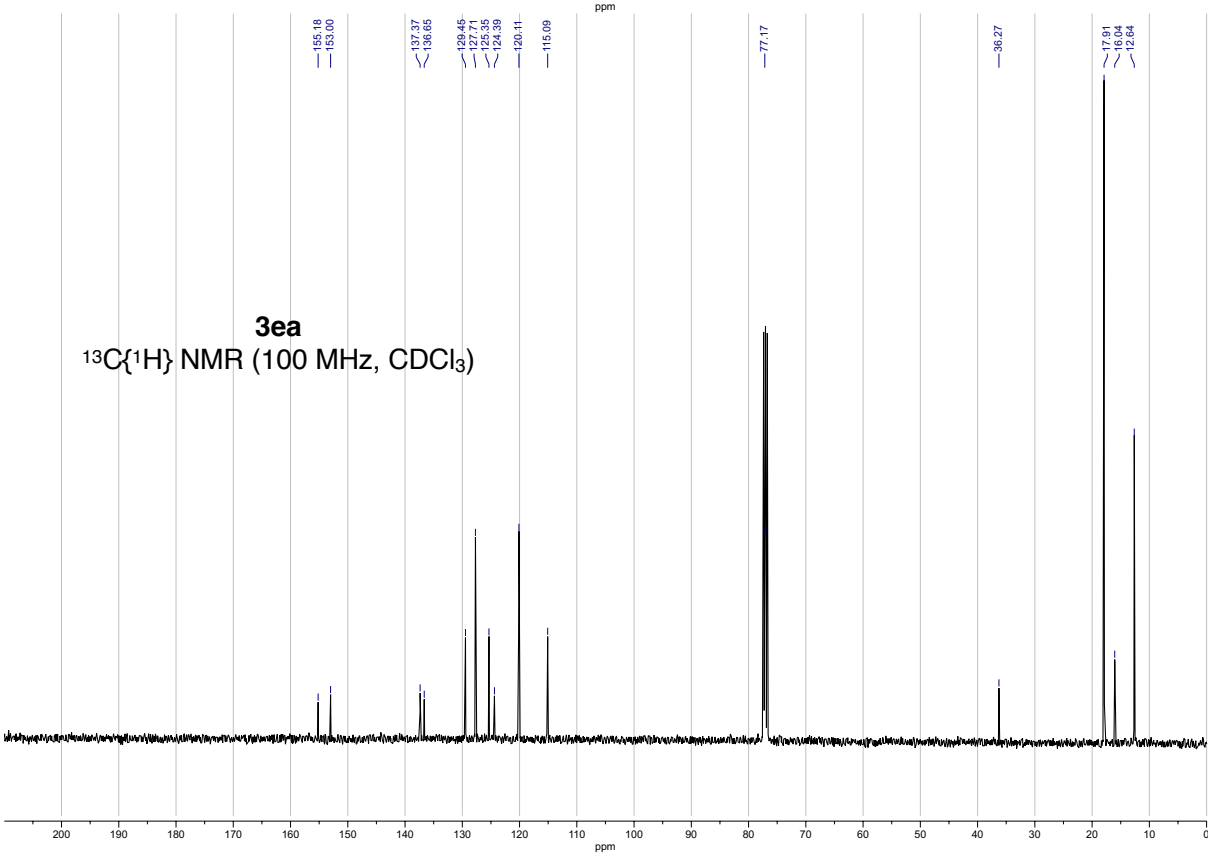

MeO
Me
OH
3ca
1H NMR (400 MHz, CDCl3)
ppm

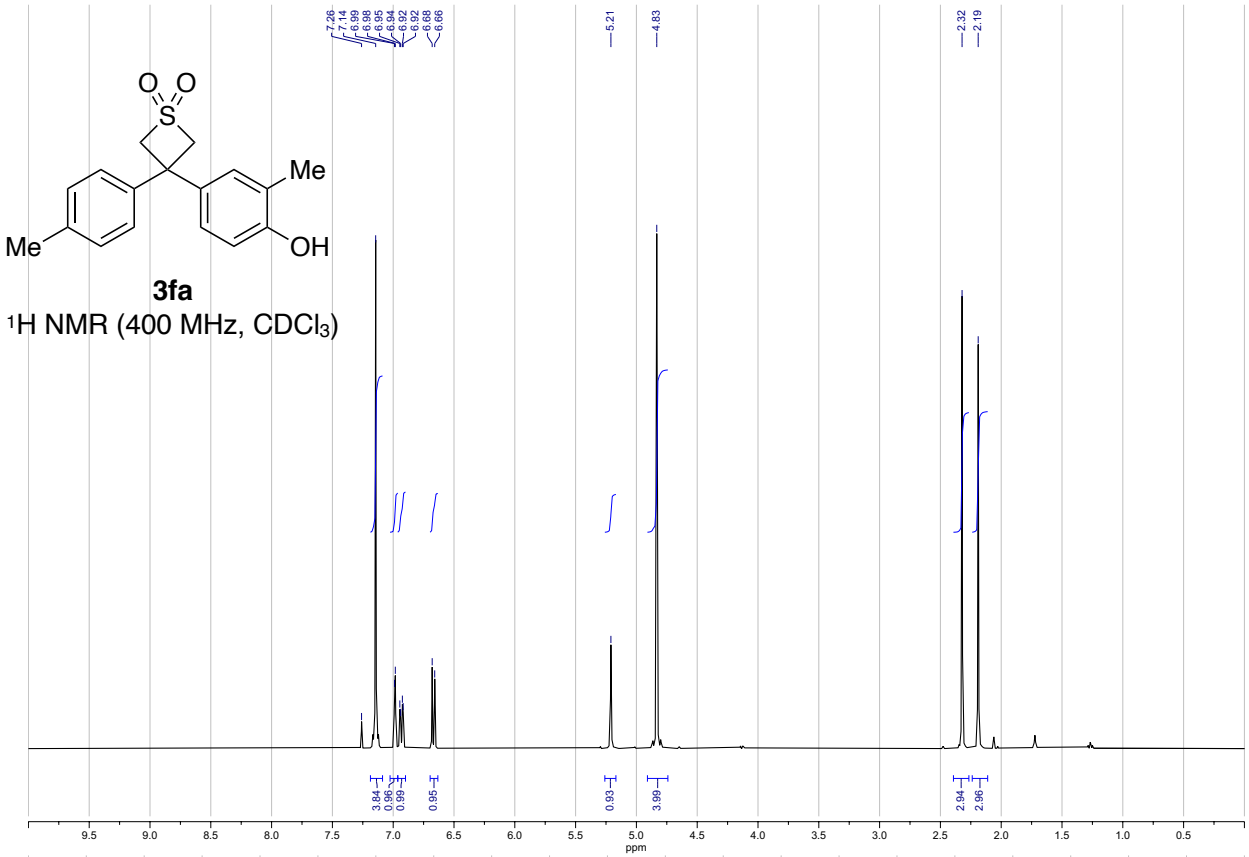

3ca
13C{1H} NMR (100 MHz, CDCl3)
ppm


Me
OH
3da
1H NMR (400 MHz, CDCl3)
ppm


3da
13C{1H} NMR (100 MHz, CDCl3)
ppm

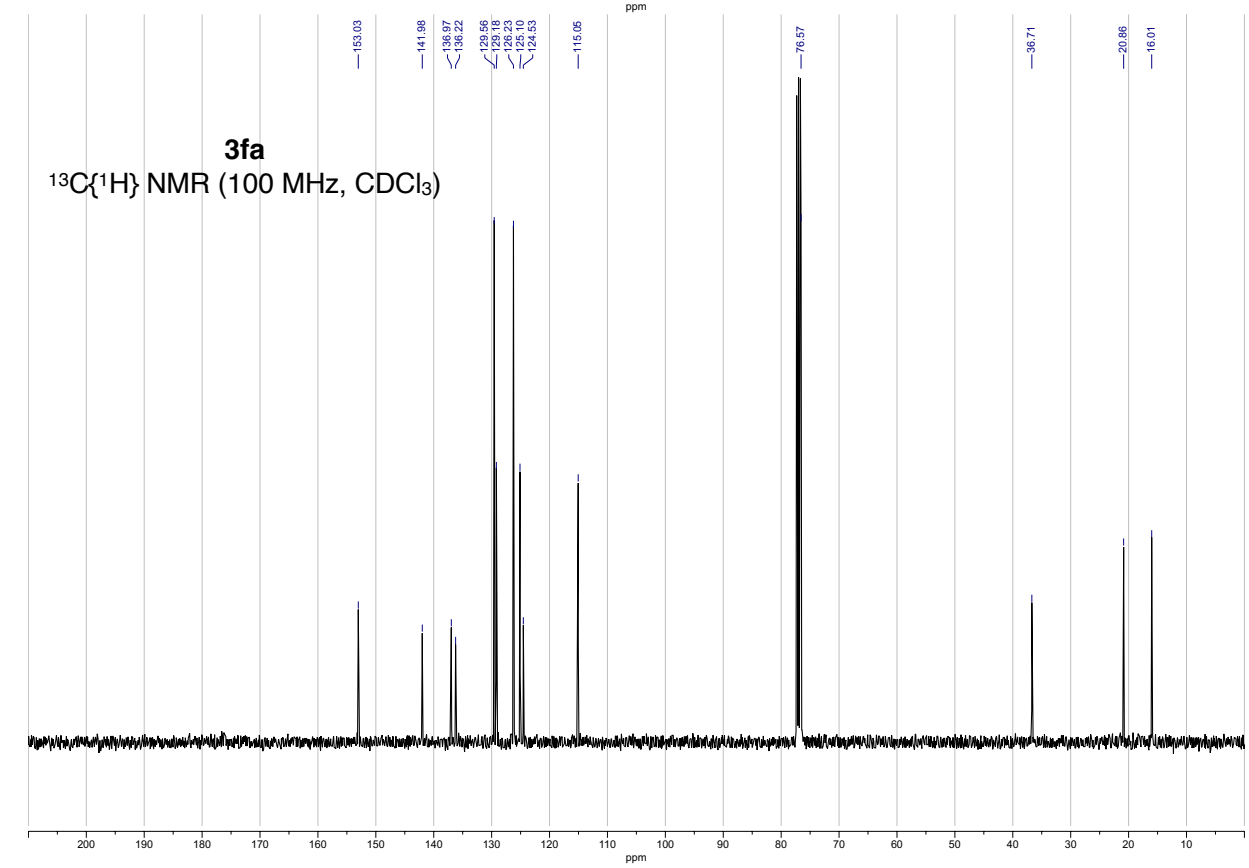

TIPSO
Me
OH
3ea
^{1}H NMR (400 MHz, CDCl$_3$)
ppm


3ea
^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$)
ppm



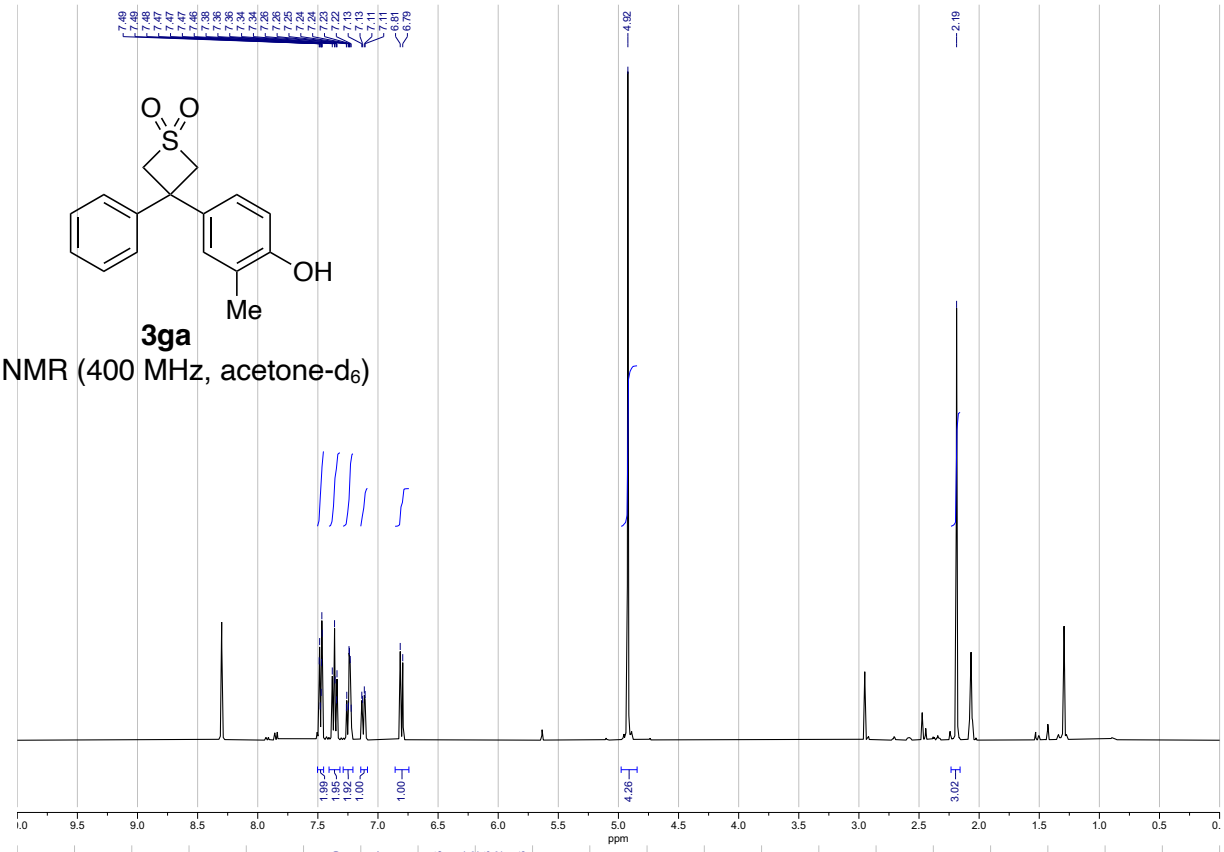
3fa

^{1}H NMR (400 MHz, $CDCl_3$)



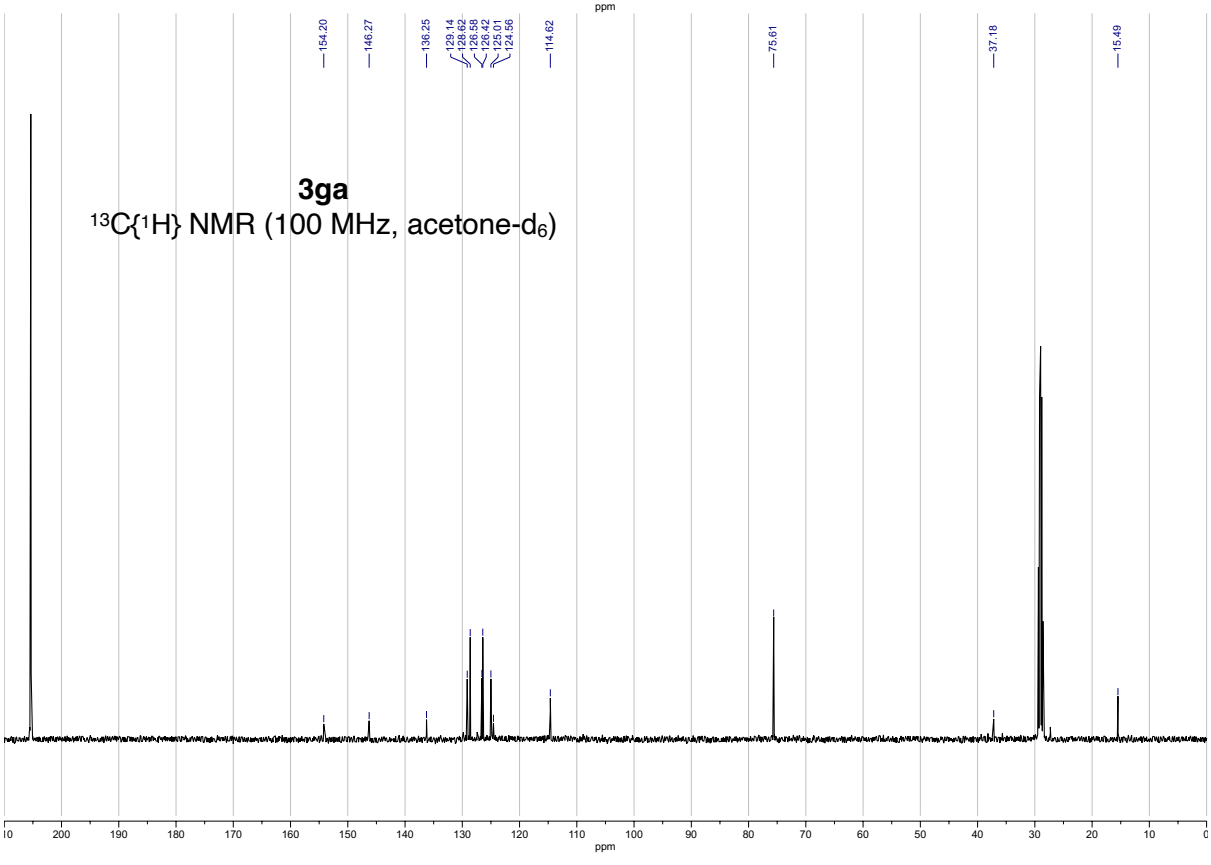
3fa

$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$)



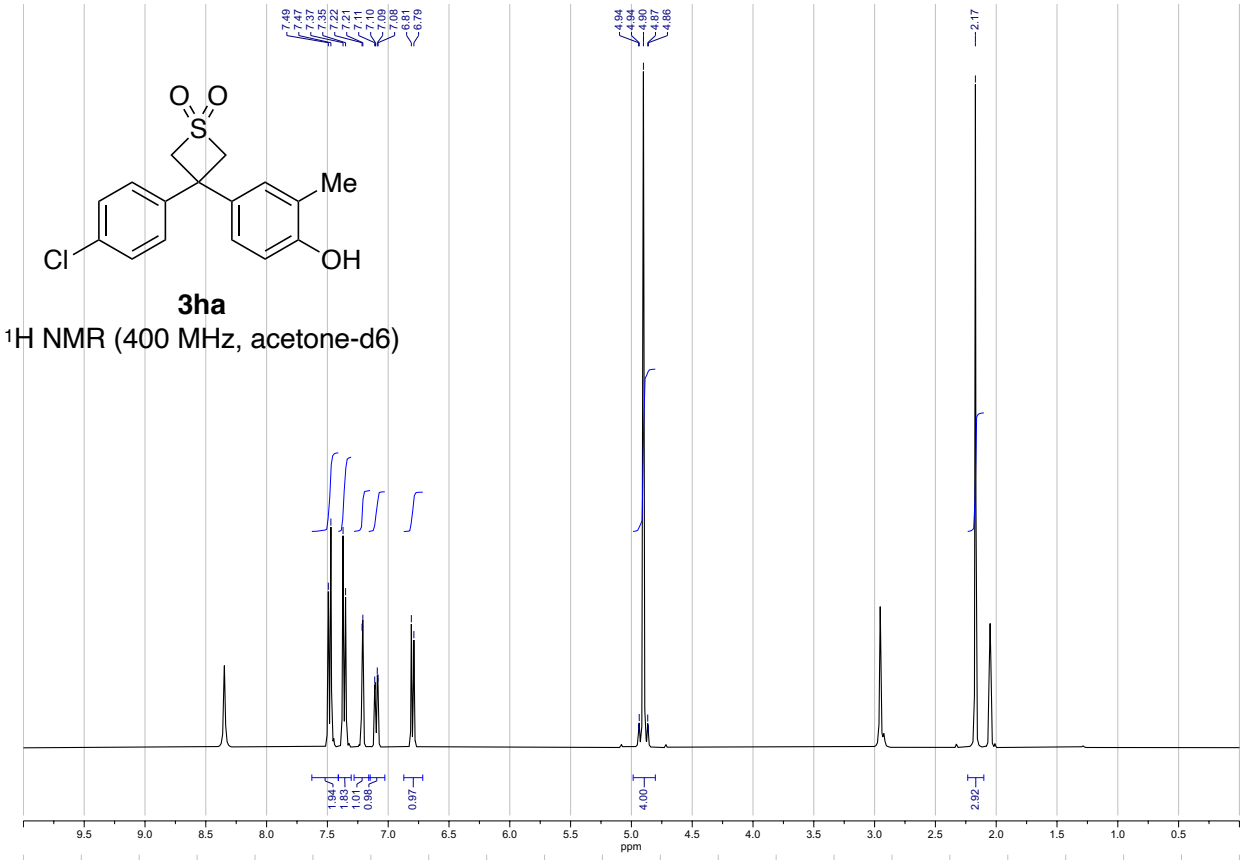
3ga

^{1}H NMR (400 MHz, acetone-d_6)



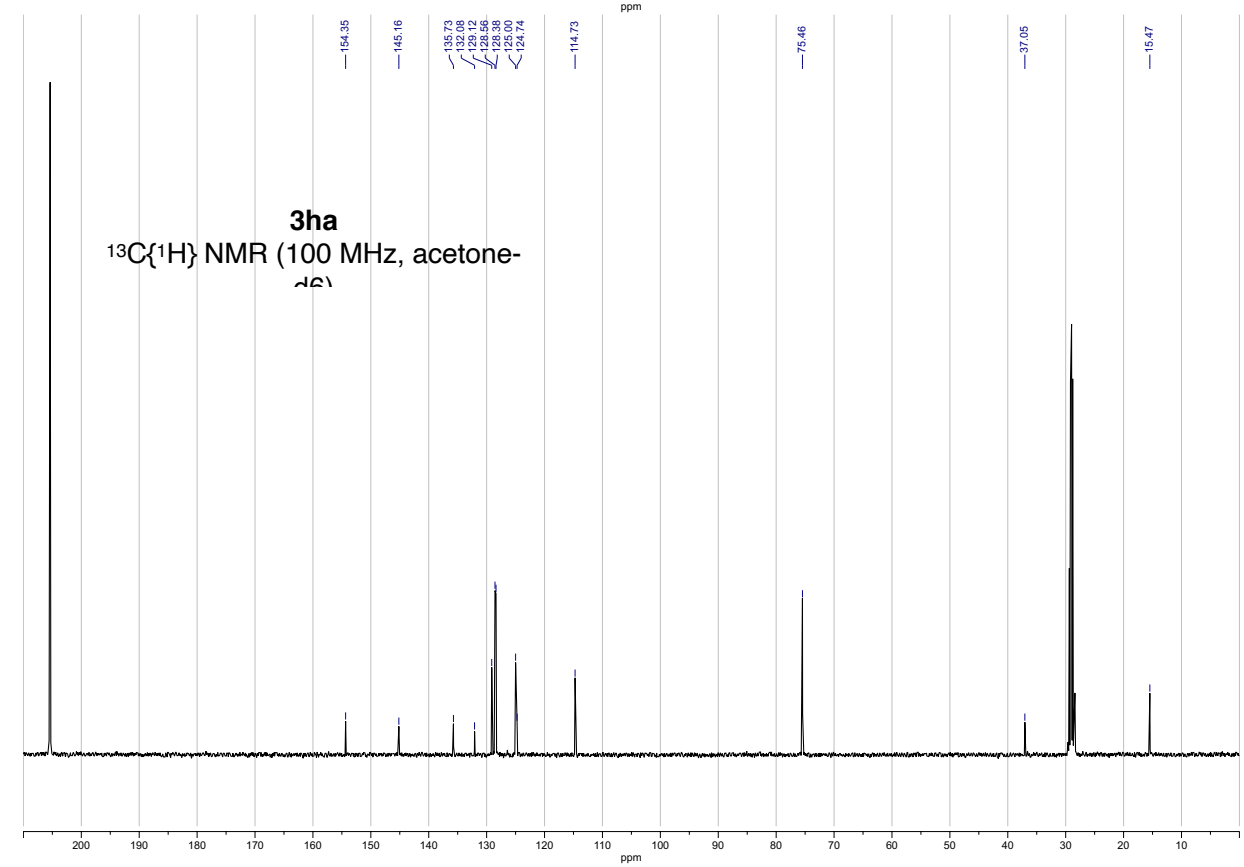
3ga

^{13}C{^{1}H} NMR (100 MHz, acetone-d_6)



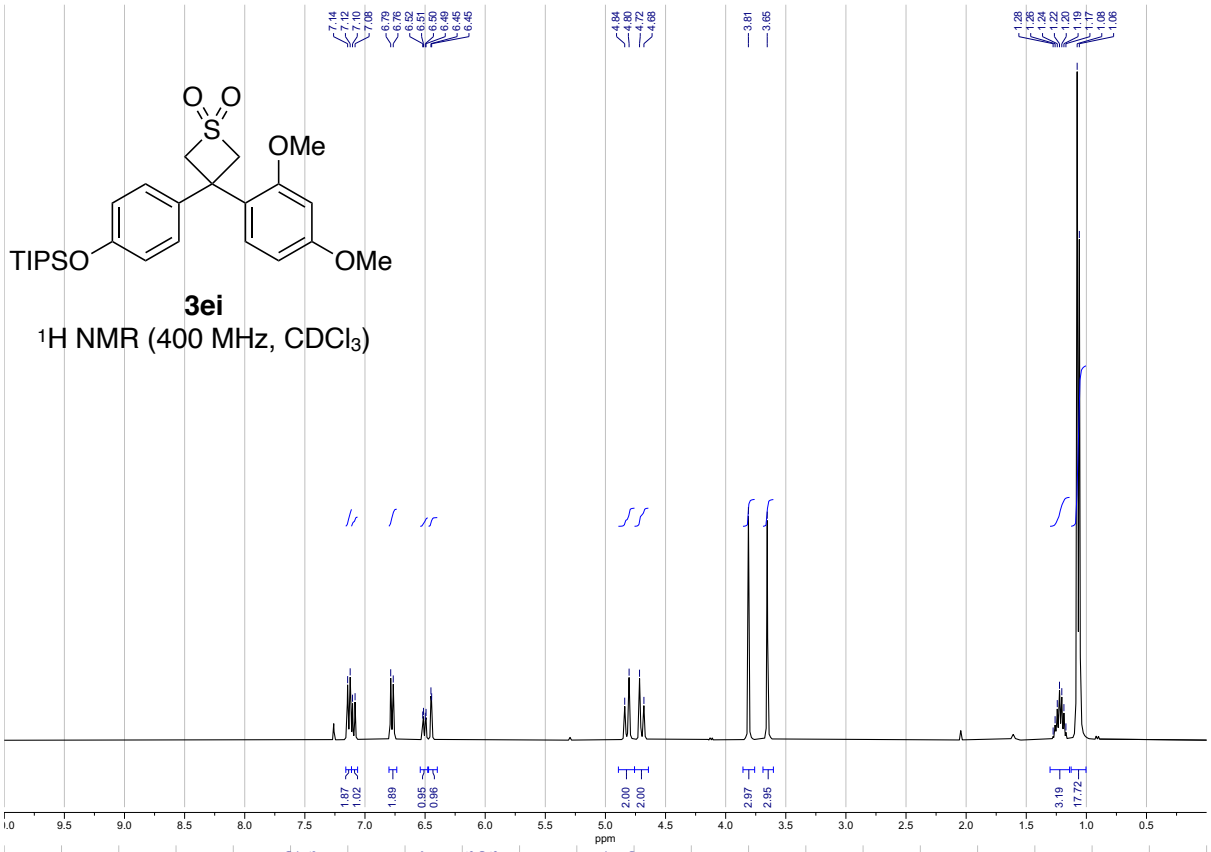
3ha

^{1}H NMR (400 MHz, acetone-d6)



3ha

^{13}C{^{1}H} NMR (100 MHz, acetone-d6)

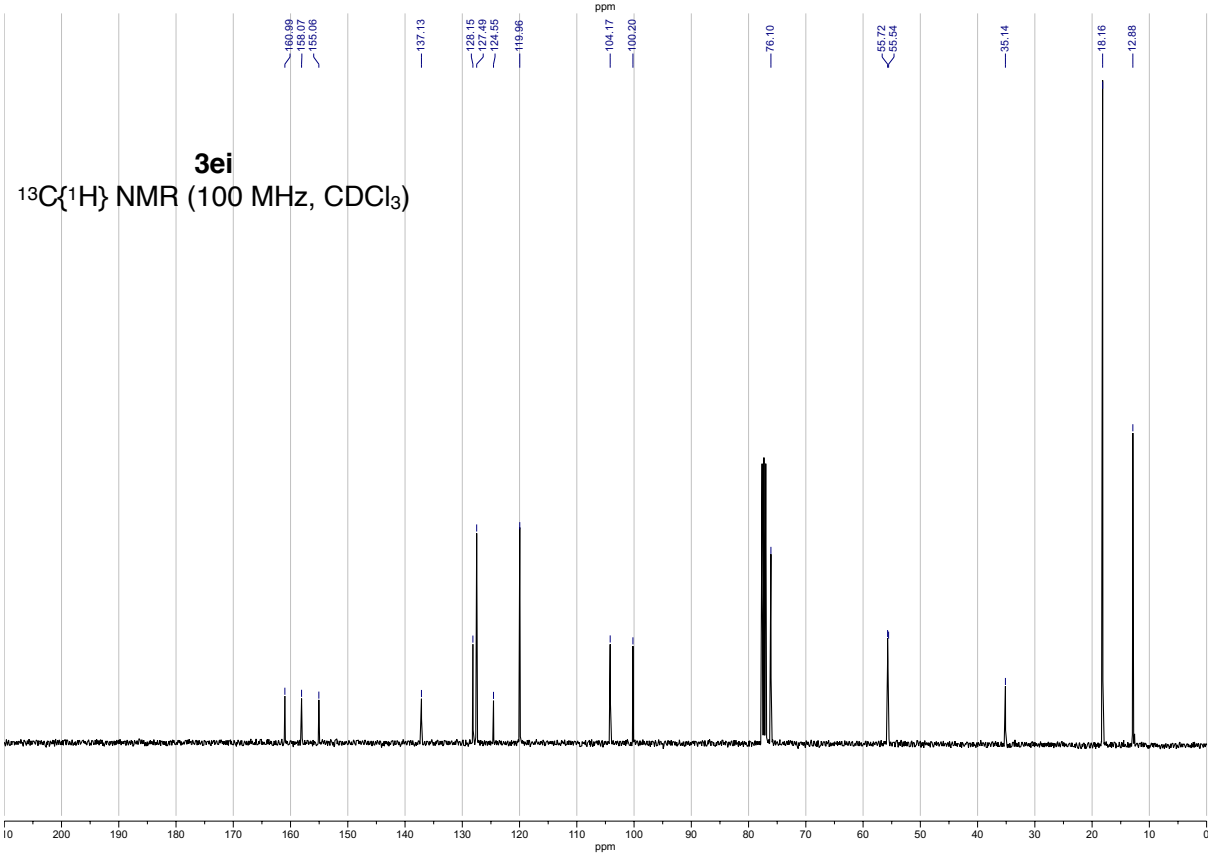


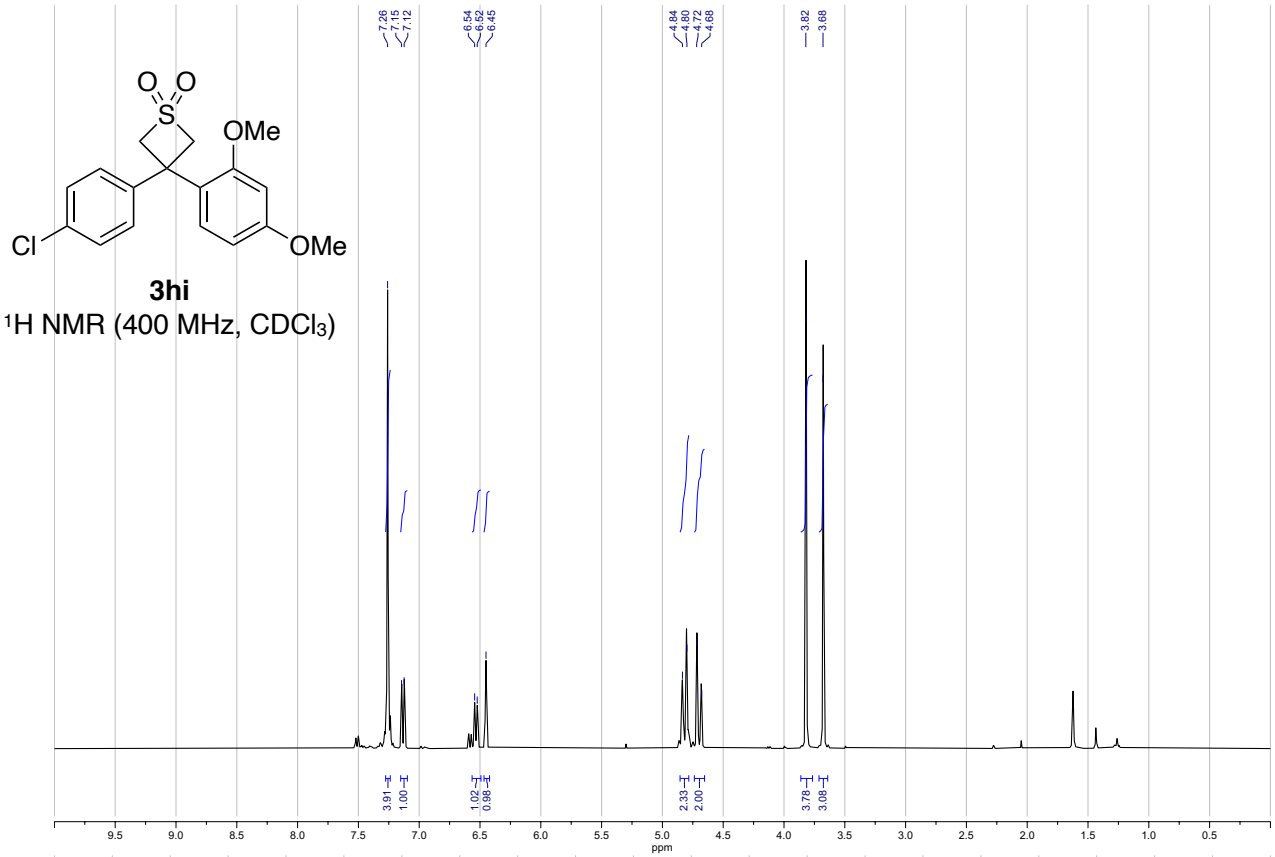
3ei

^{1}H NMR (400 MHz, $CDCl_3$)

3ei

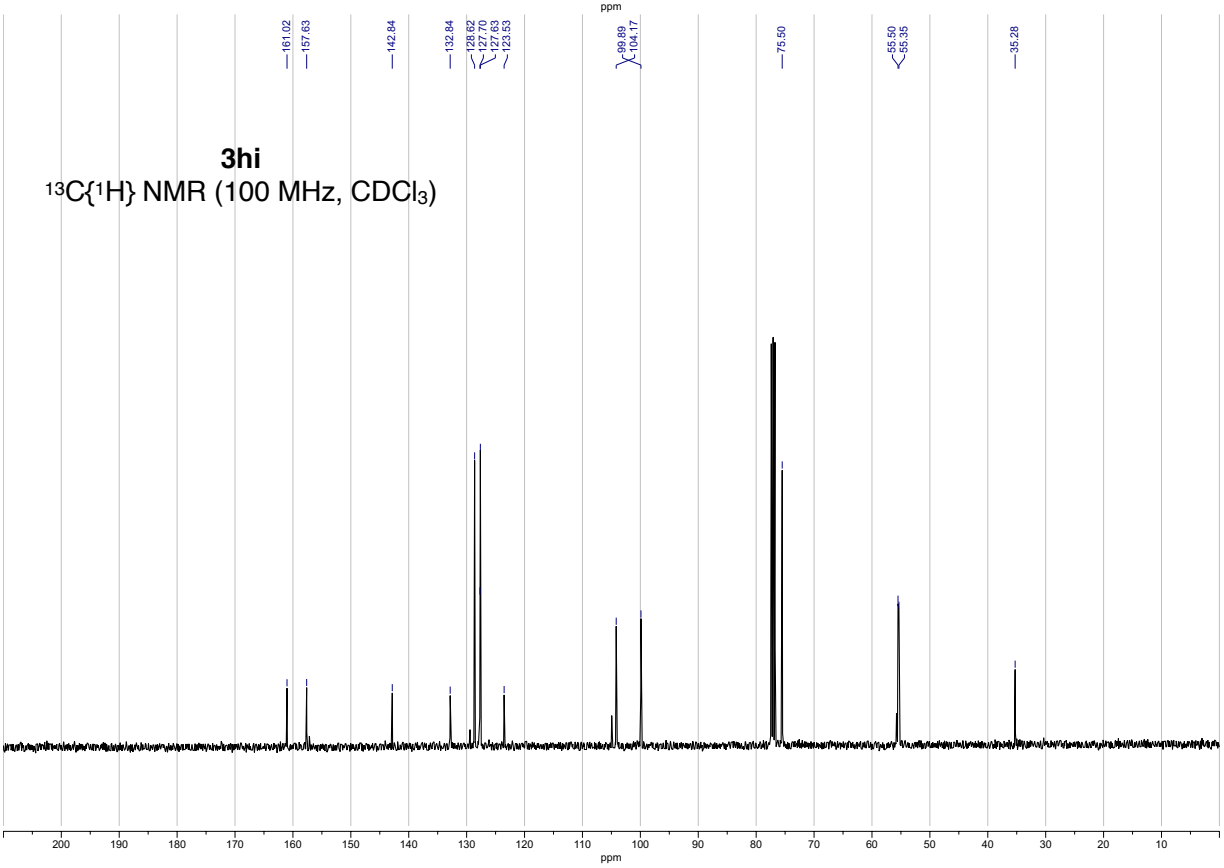
$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$)





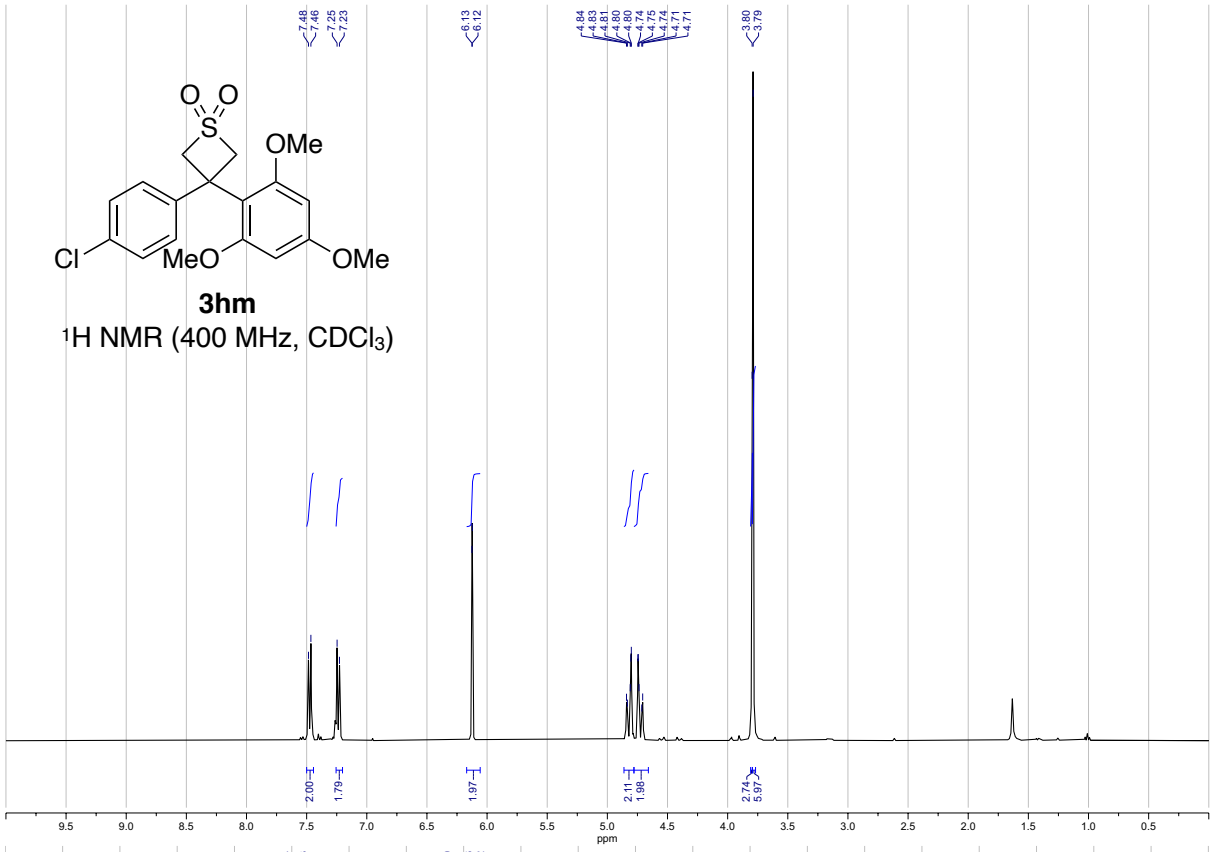
3hi

^{1}H NMR (400 MHz, $CDCl_3$)



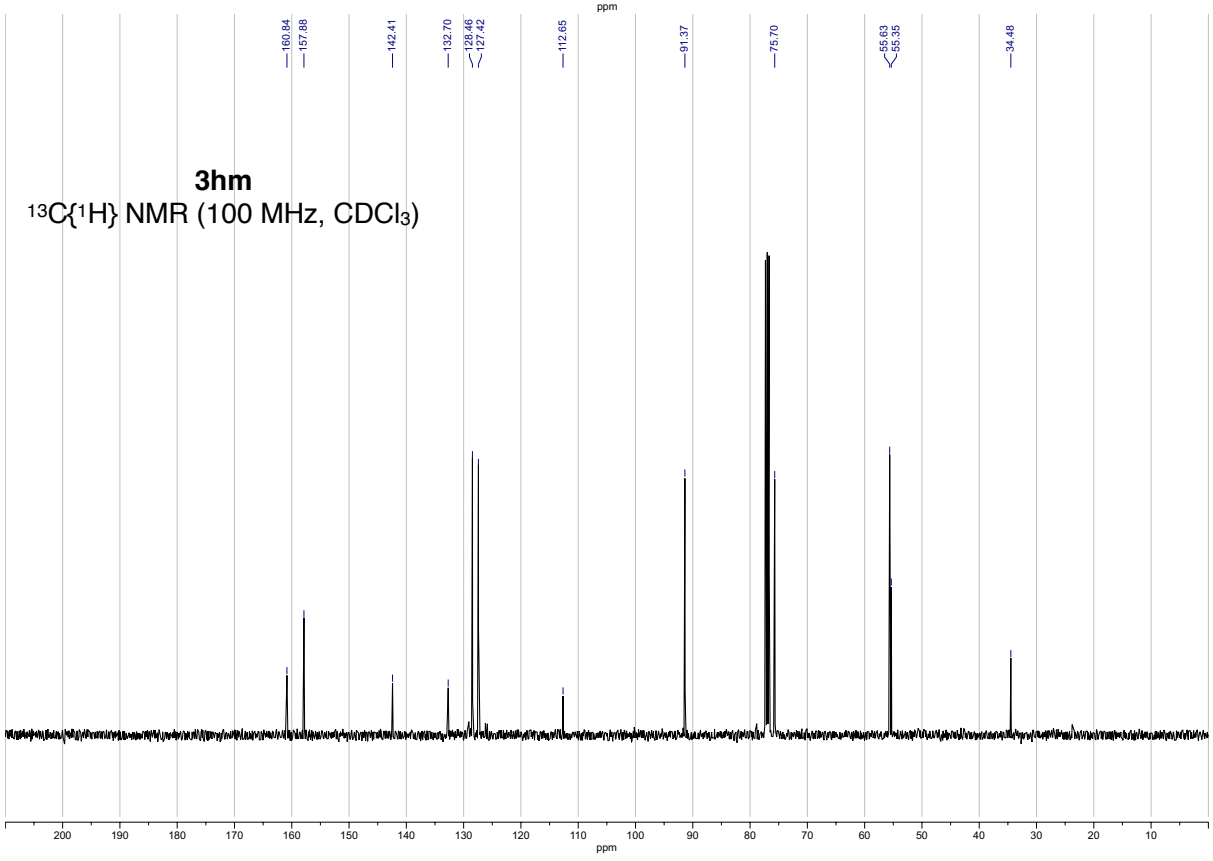
3hi

$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$)



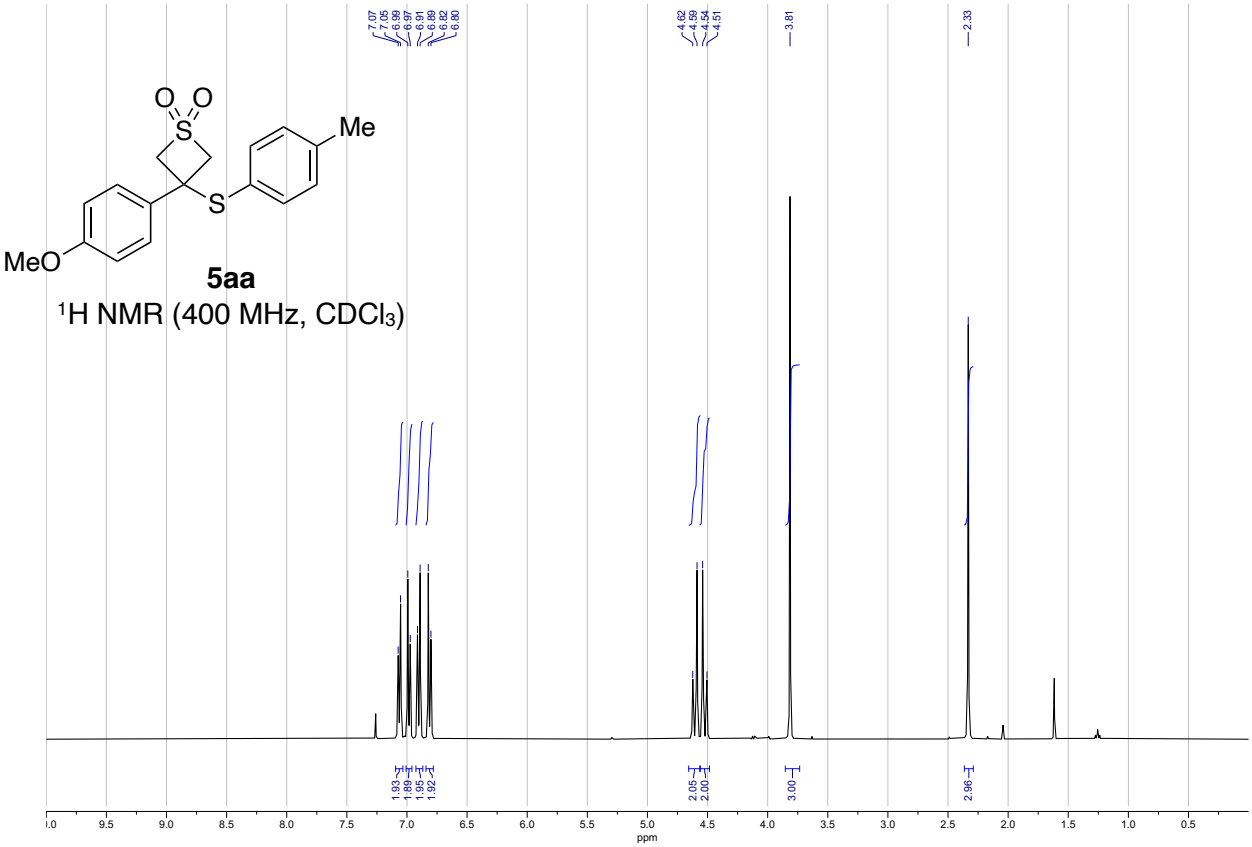
3hm

^{1}H NMR (400 MHz, $CDCl_3$)



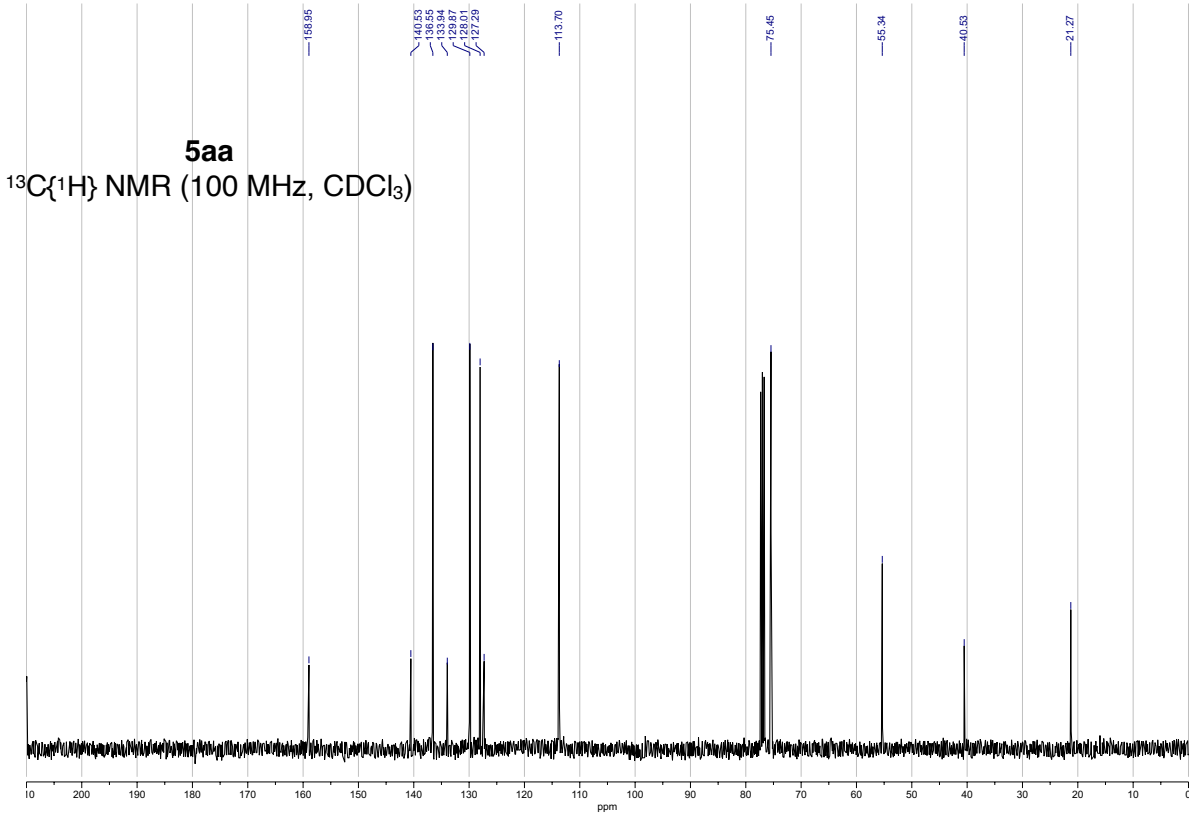
3hm

$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$)



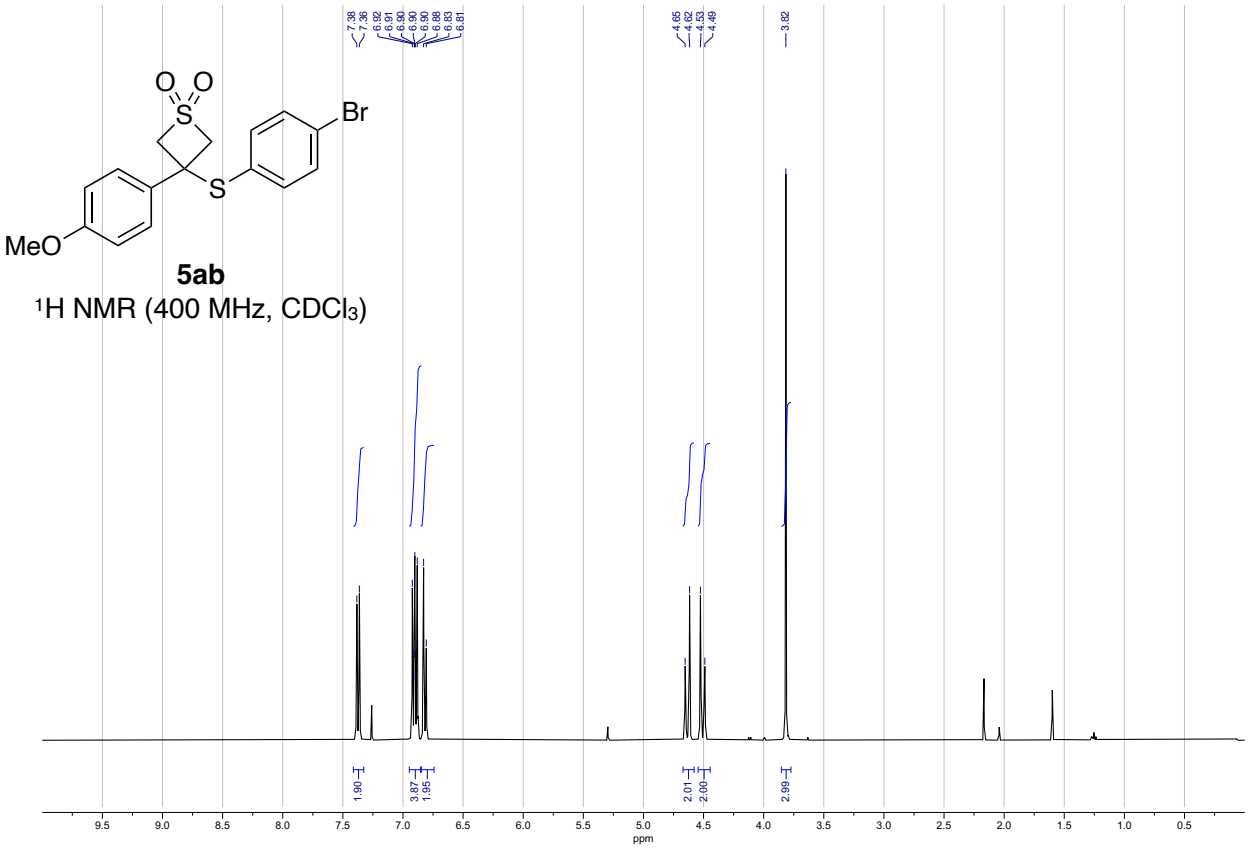
5aa

^{1}H NMR (400 MHz, $CDCl_3$)



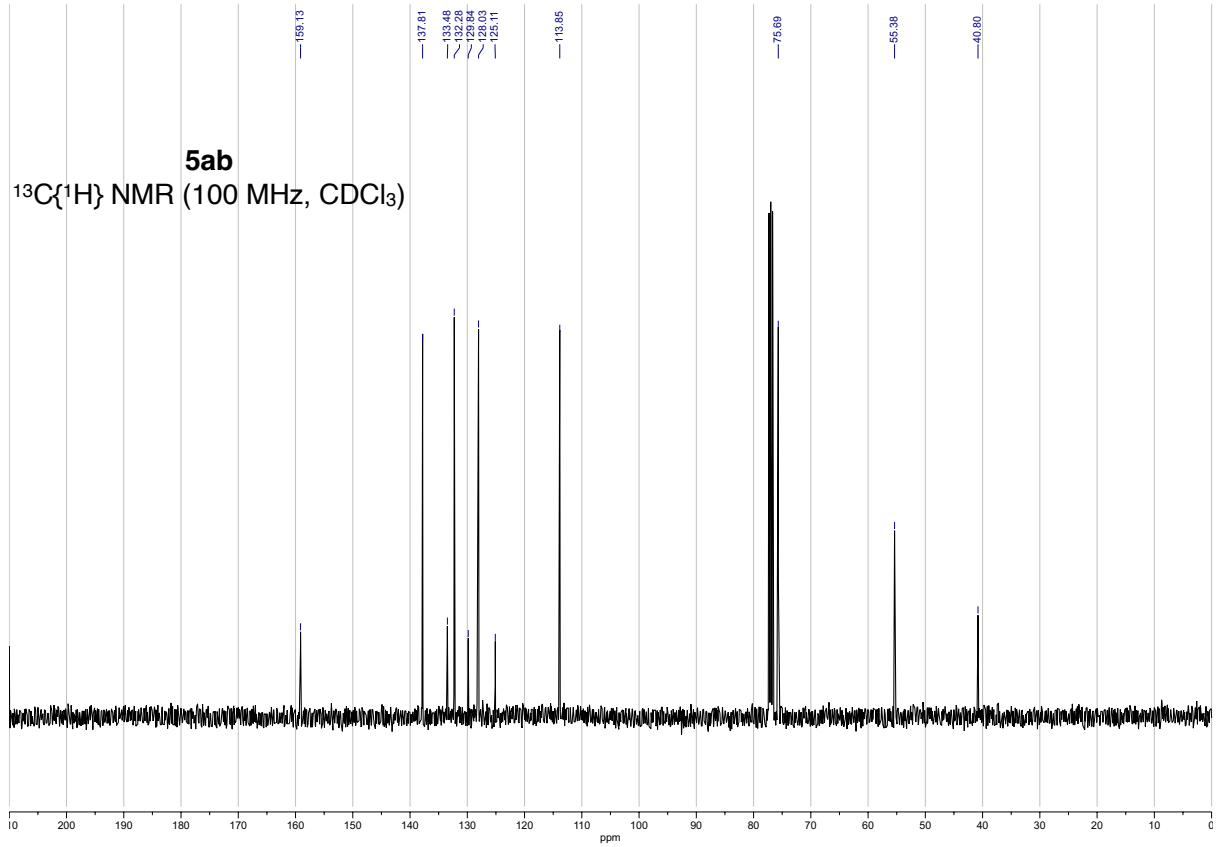
5aa

$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$)



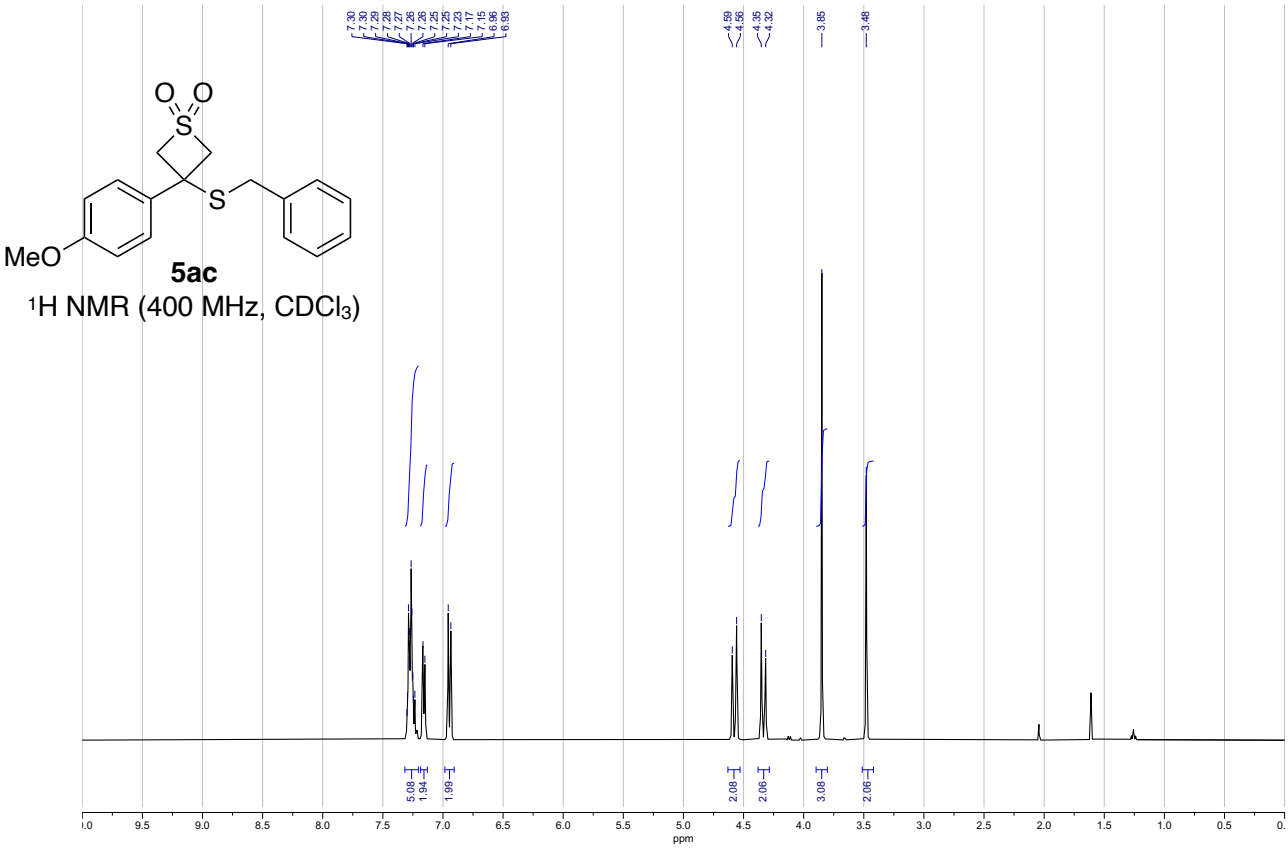
5ab

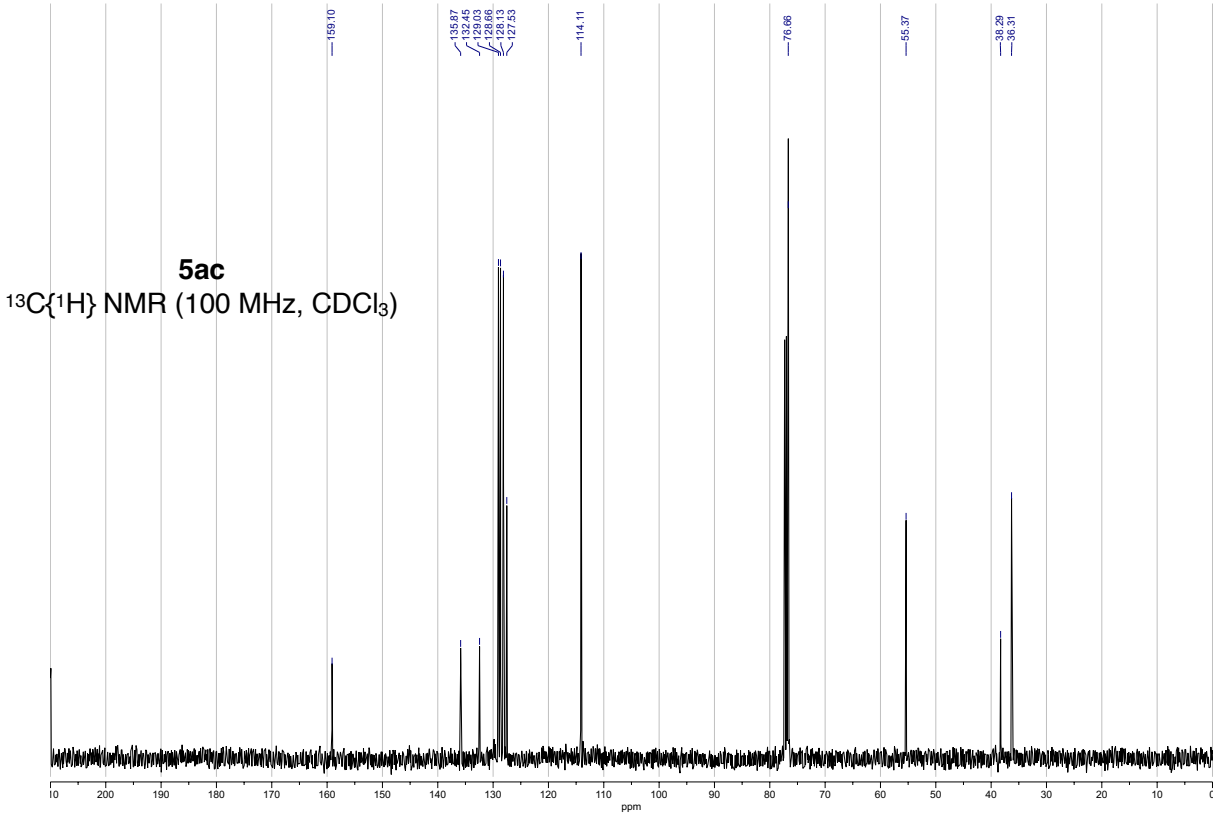
^{1}H NMR (400 MHz, $CDCl_3$)

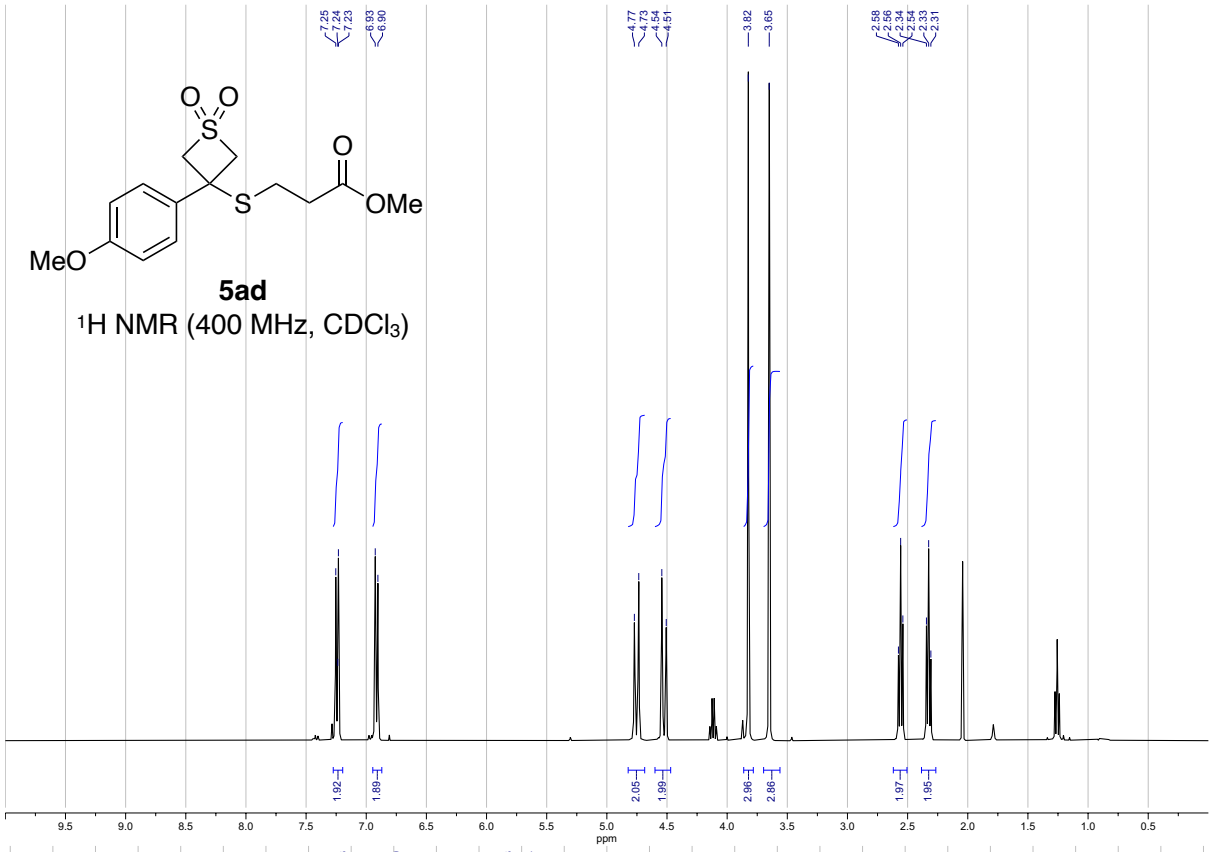


5ab

$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$)

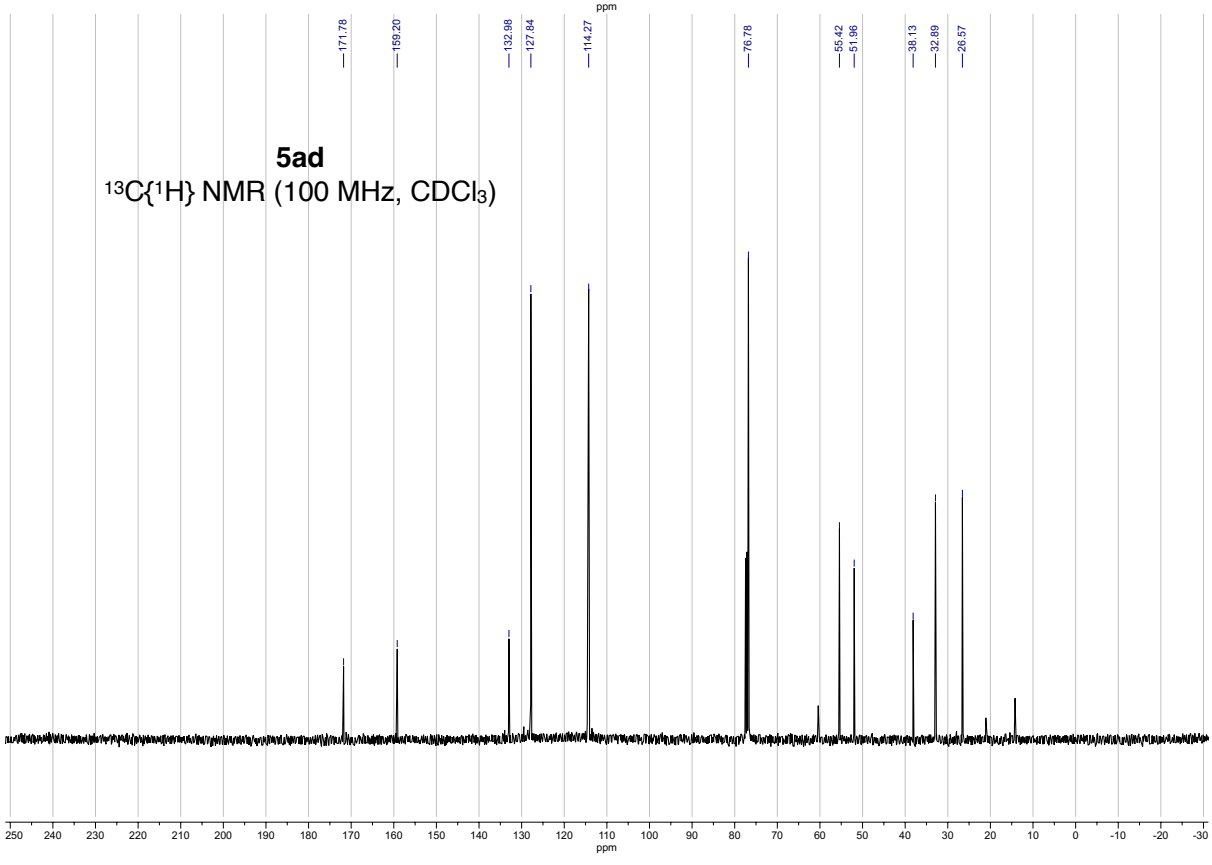

MeO
5ac
^{1}H NMR (400 MHz, $CDCl_3$)
ppm


5ac
$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$)
ppm



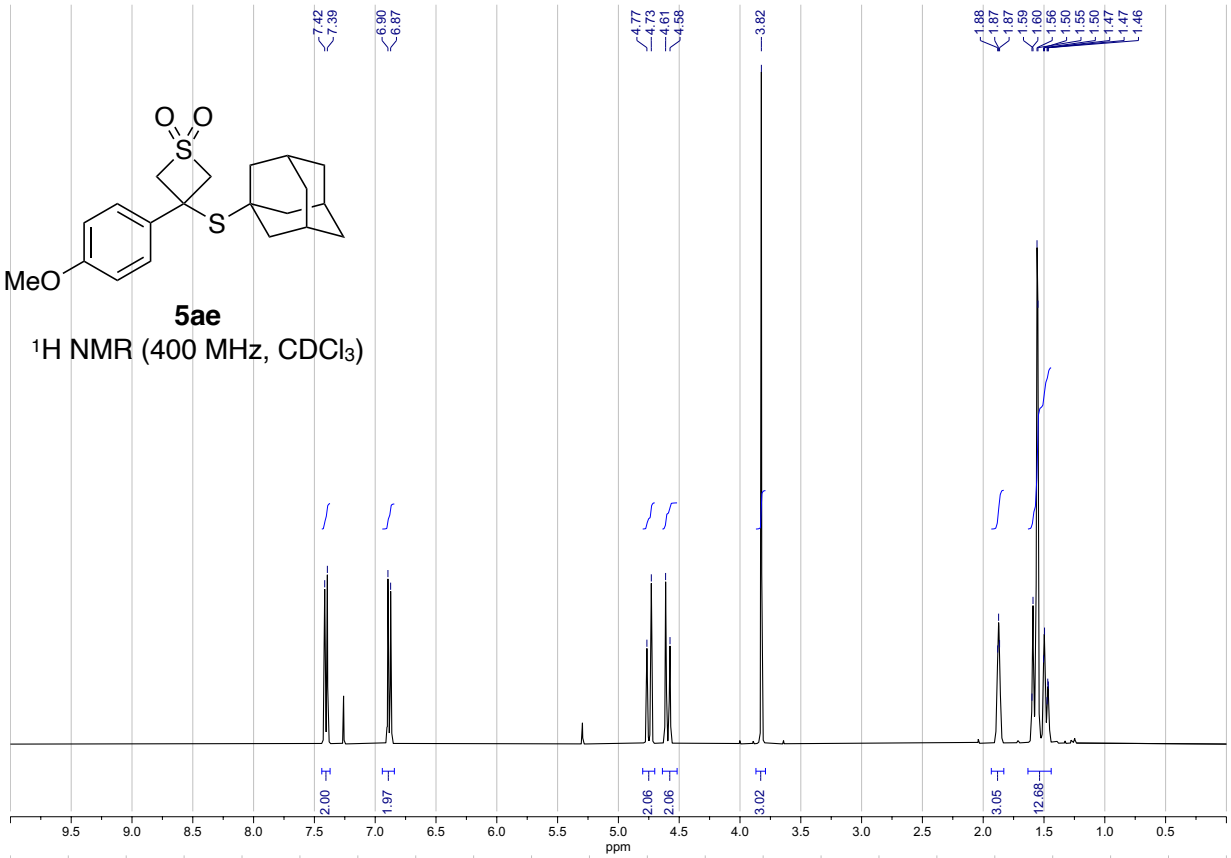
5ad

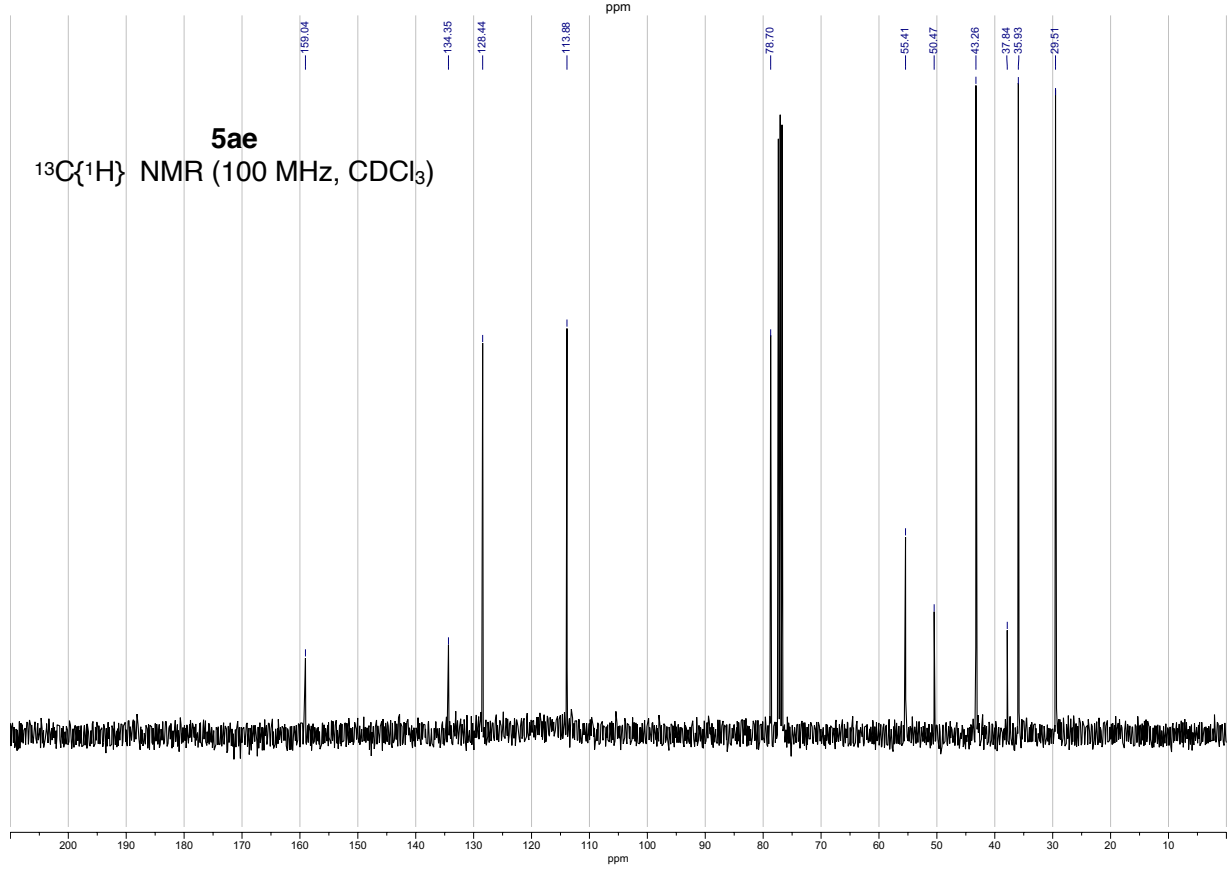
^{1}H NMR (400 MHz, $CDCl_3$)

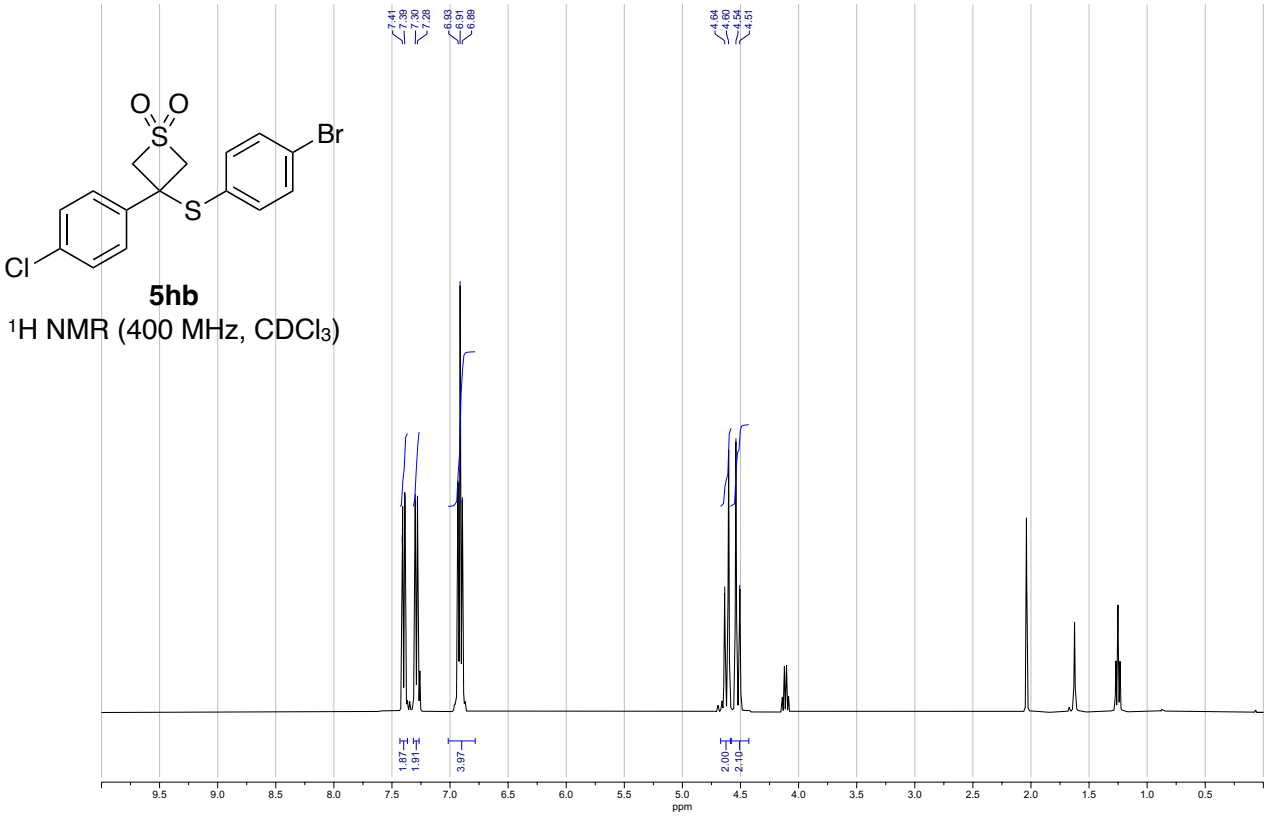


5ad

$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$)

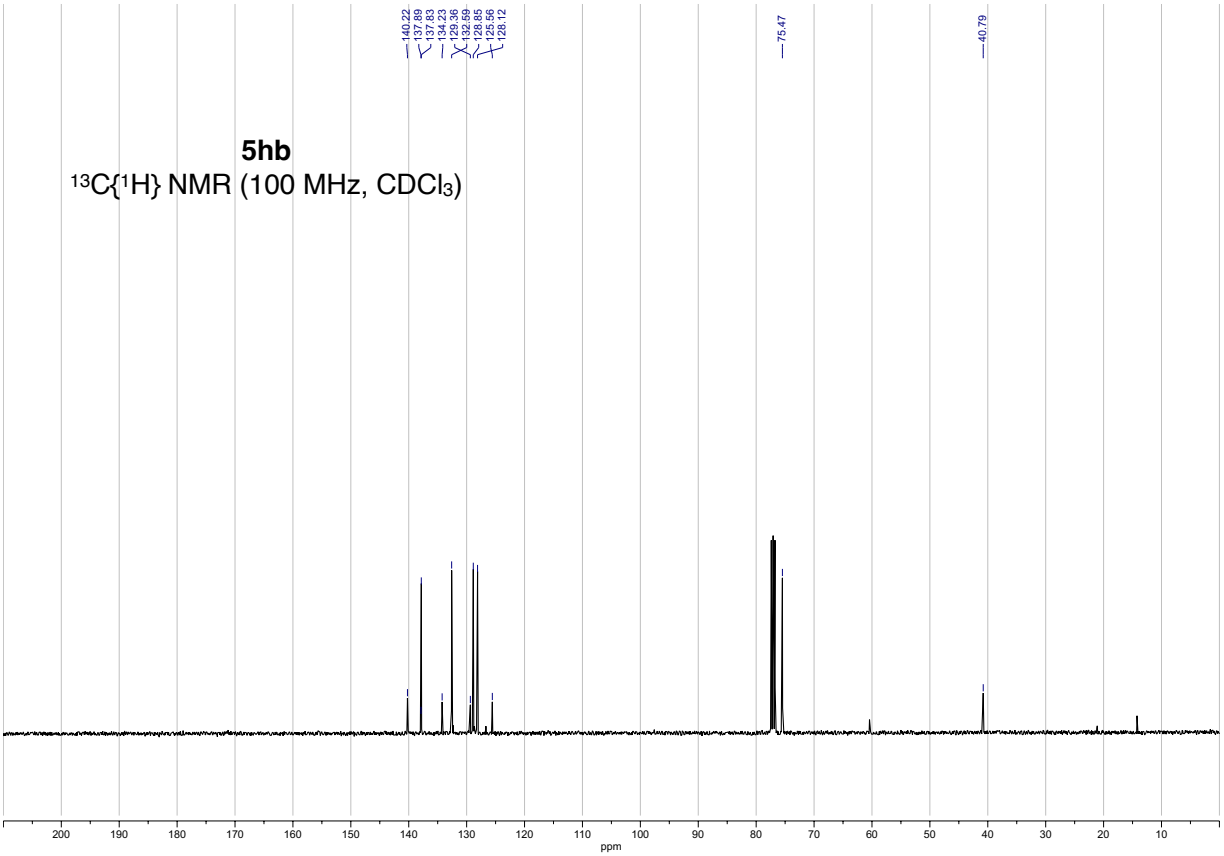

MeO
5ae
^{1}H NMR (400 MHz, CDCl$_3$)
7.42
7.39
6.90
6.87
4.77
4.73
4.61
4.58
3.82
1.88
1.87
1.87
1.59
1.60
1.56
1.50
1.55
1.50
1.47
1.47
1.46
2.00
1.97
2.06
2.06
3.02
3.05
12.68
ppm


5ae
^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$)
159.04
134.35
128.44
113.88
78.70
55.41
50.47
43.26
37.84
35.93
29.51
ppm



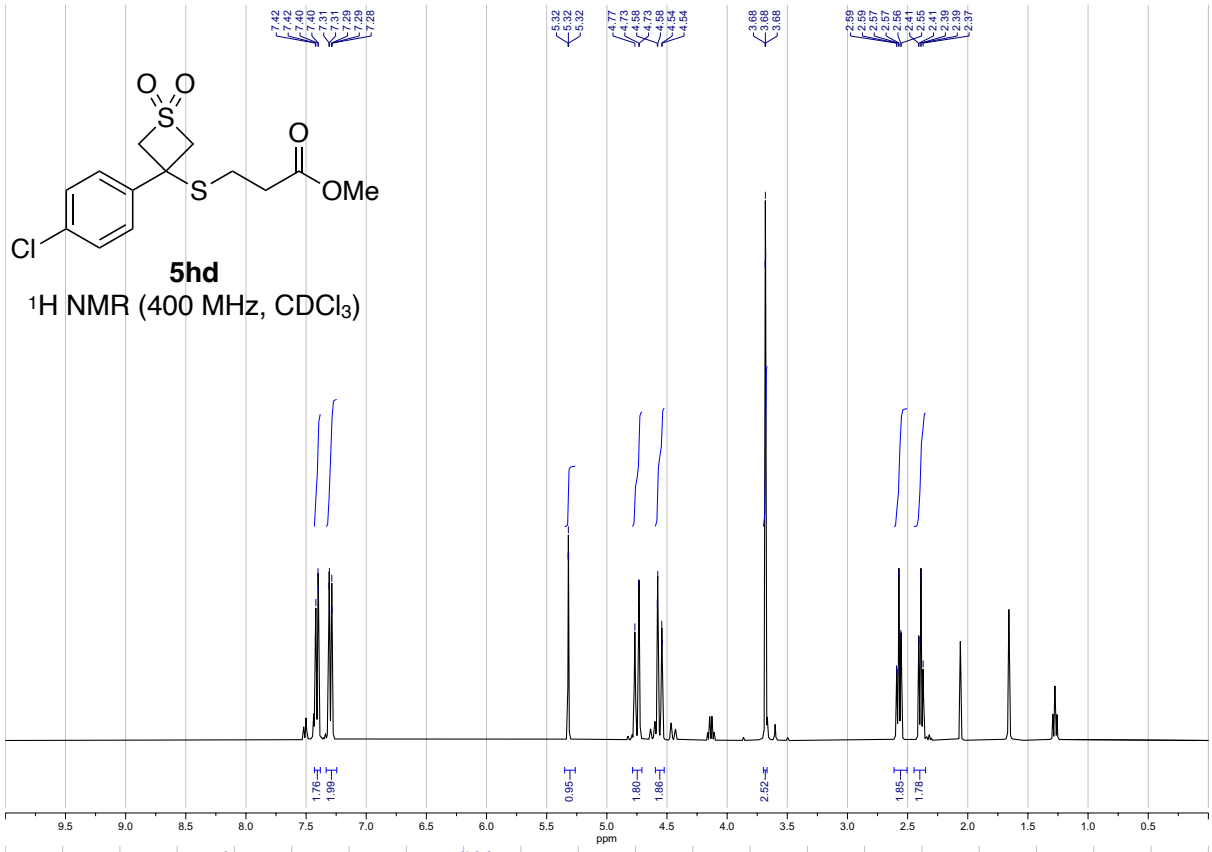
5hb

^{1}H NMR (400 MHz, $CDCl_3$)



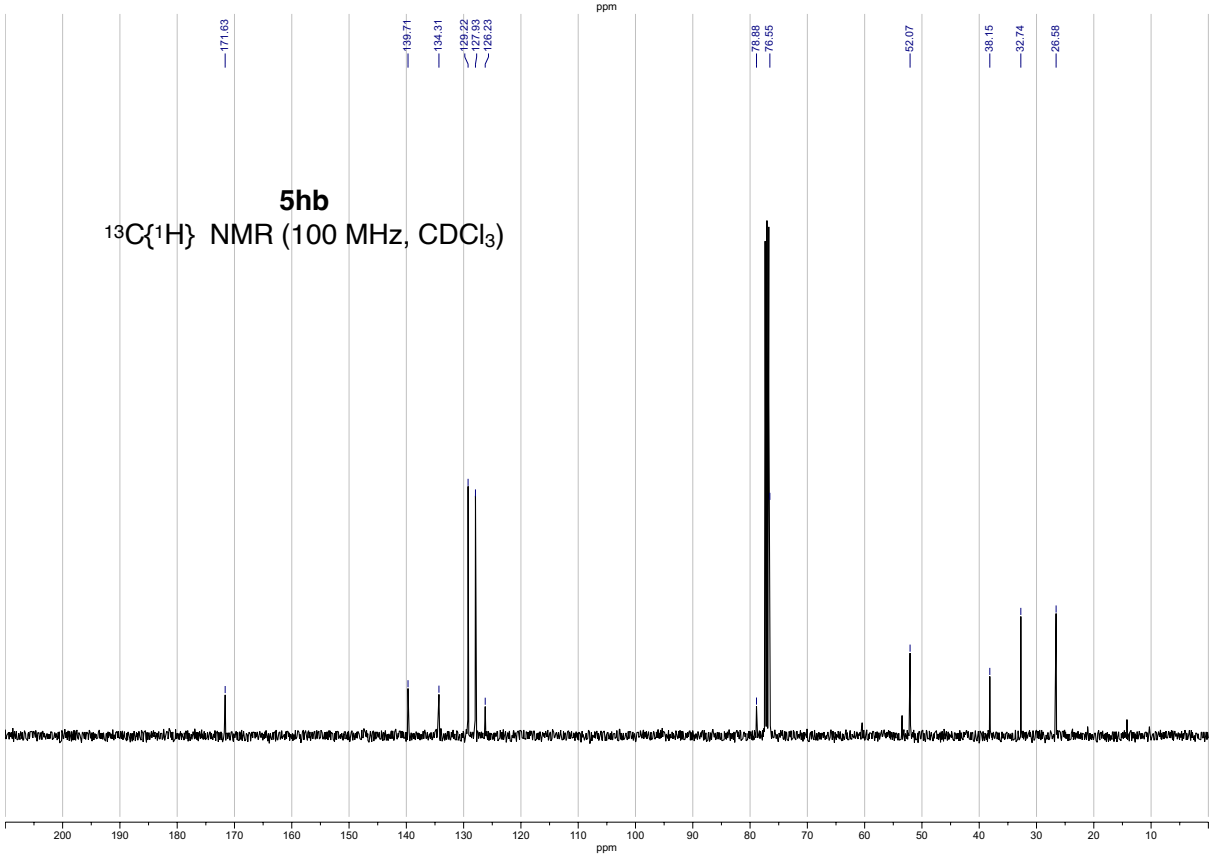
5hb

$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$)



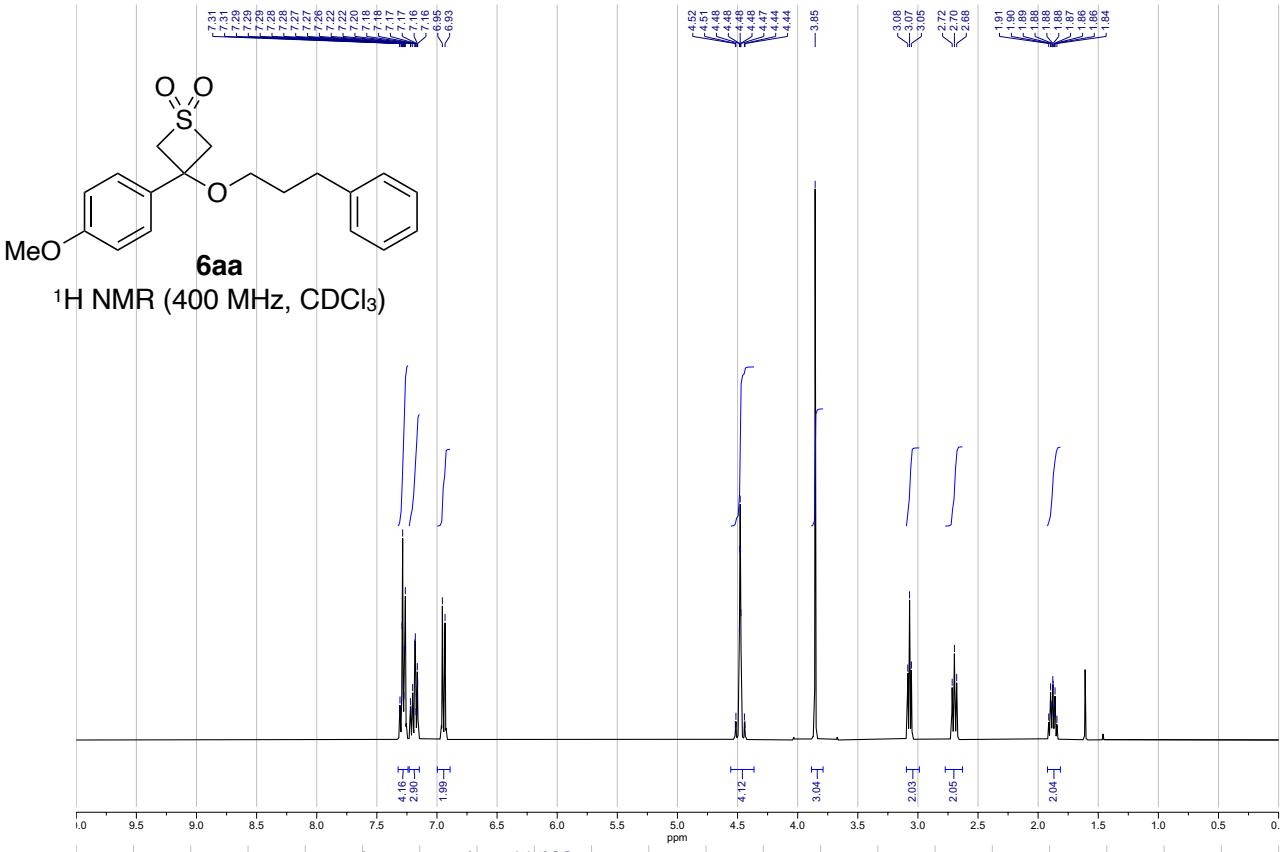
5hd

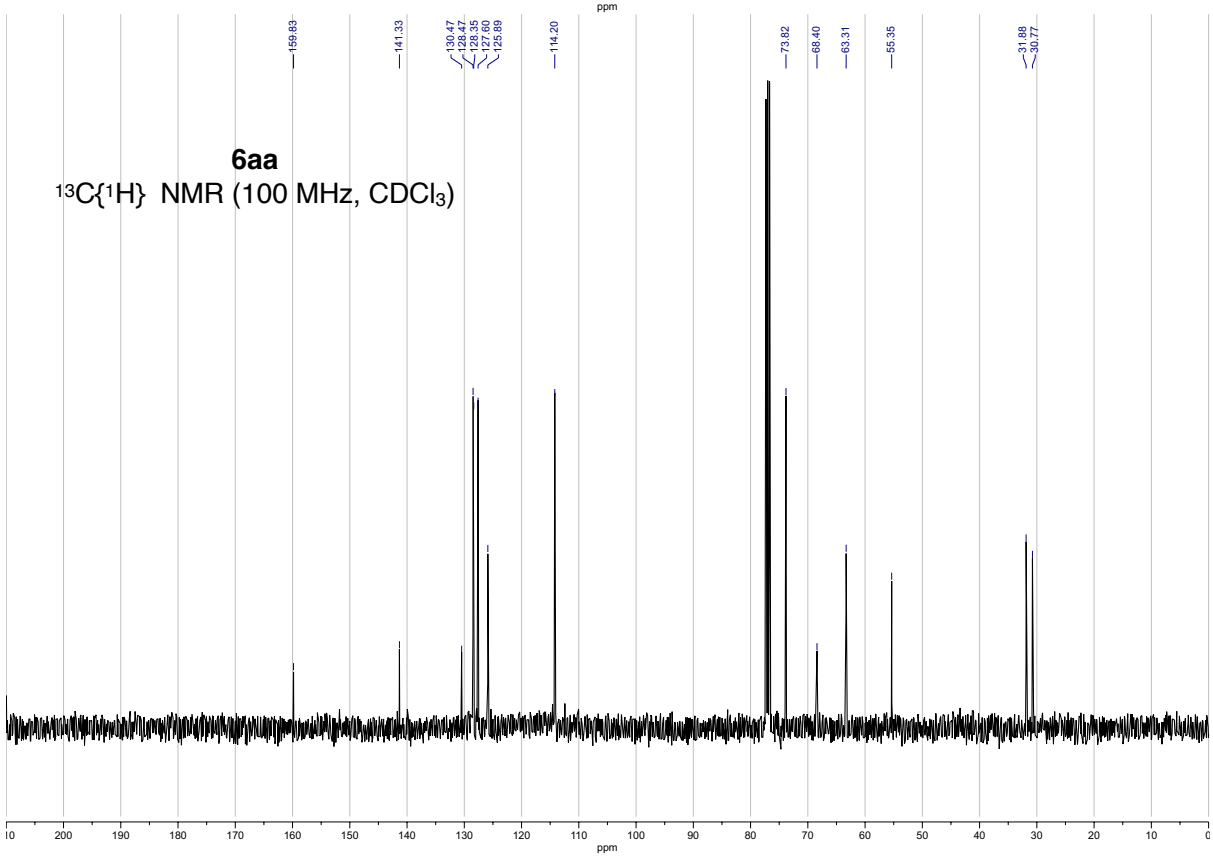
^{1}H NMR (400 MHz, $CDCl_3$)

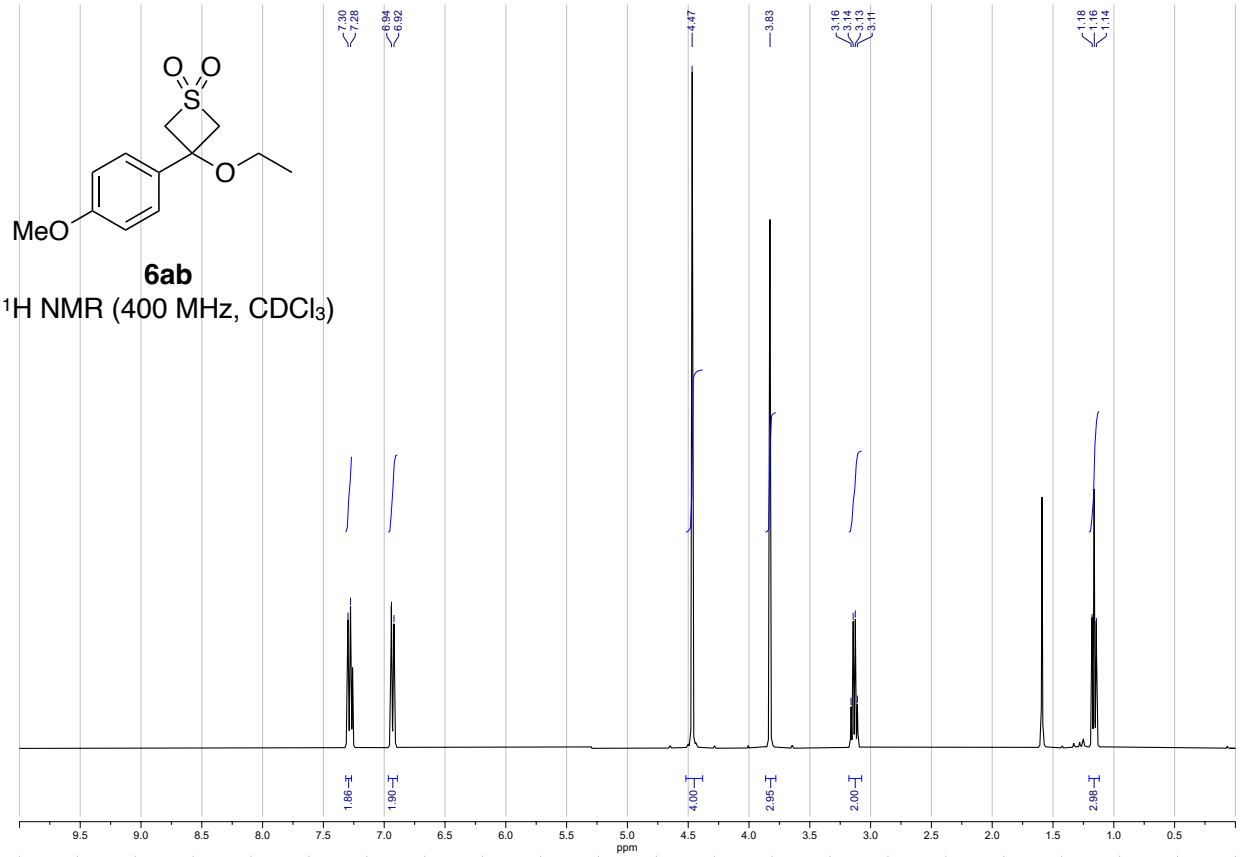


5hb

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)

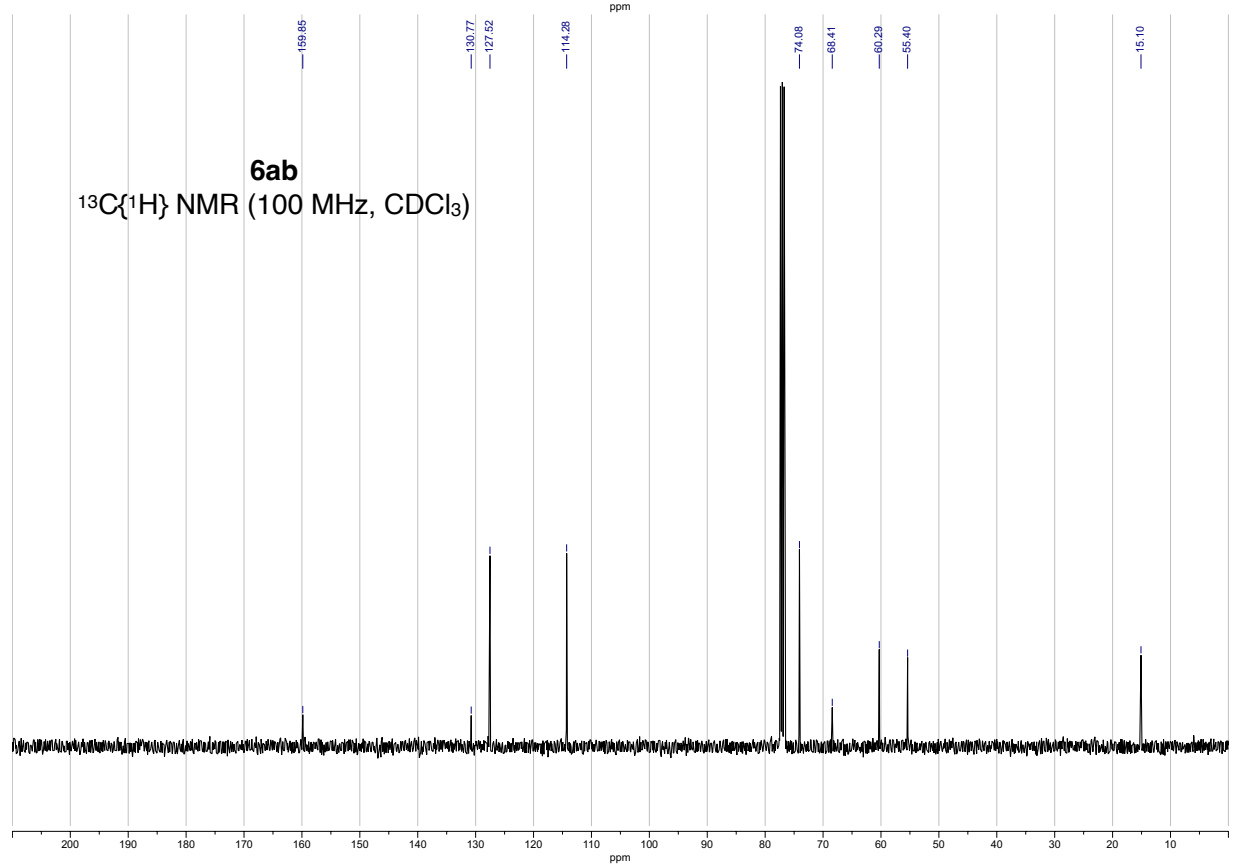

MeO
6aa
^{1}H NMR (400 MHz, $CDCl_3$)
ppm


6aa
$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$)
ppm



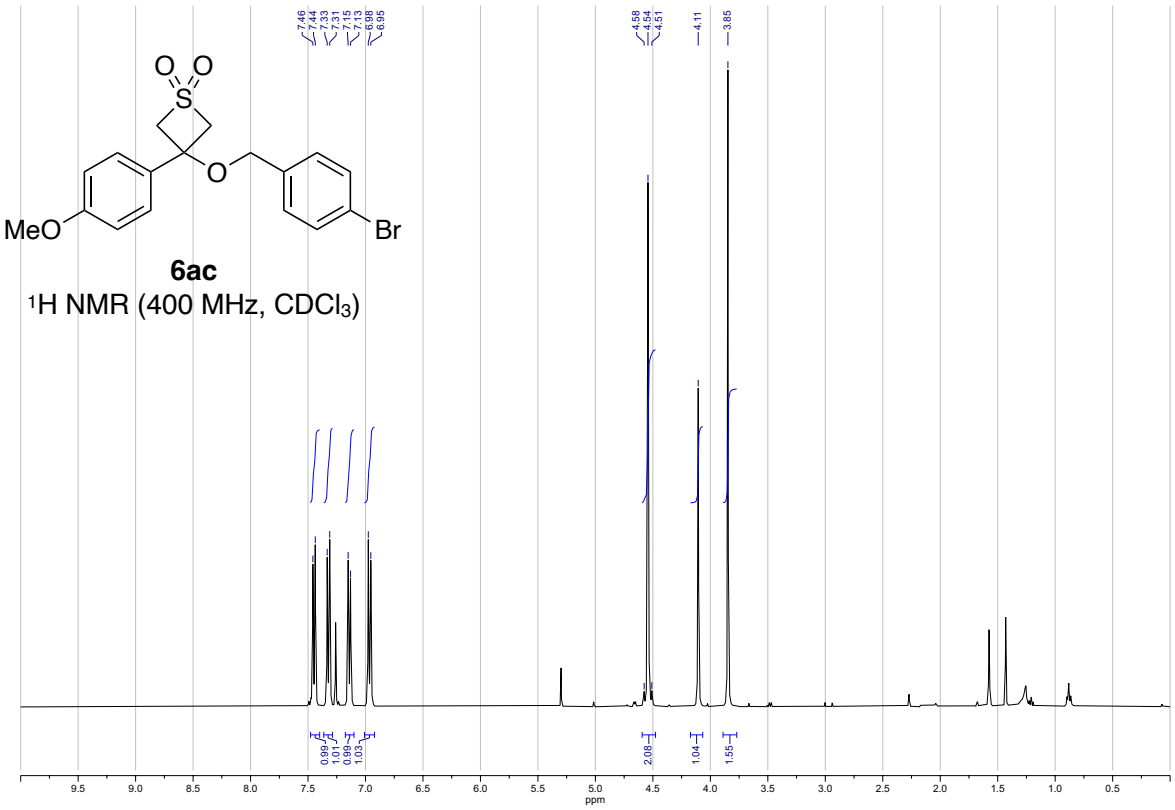
6ab

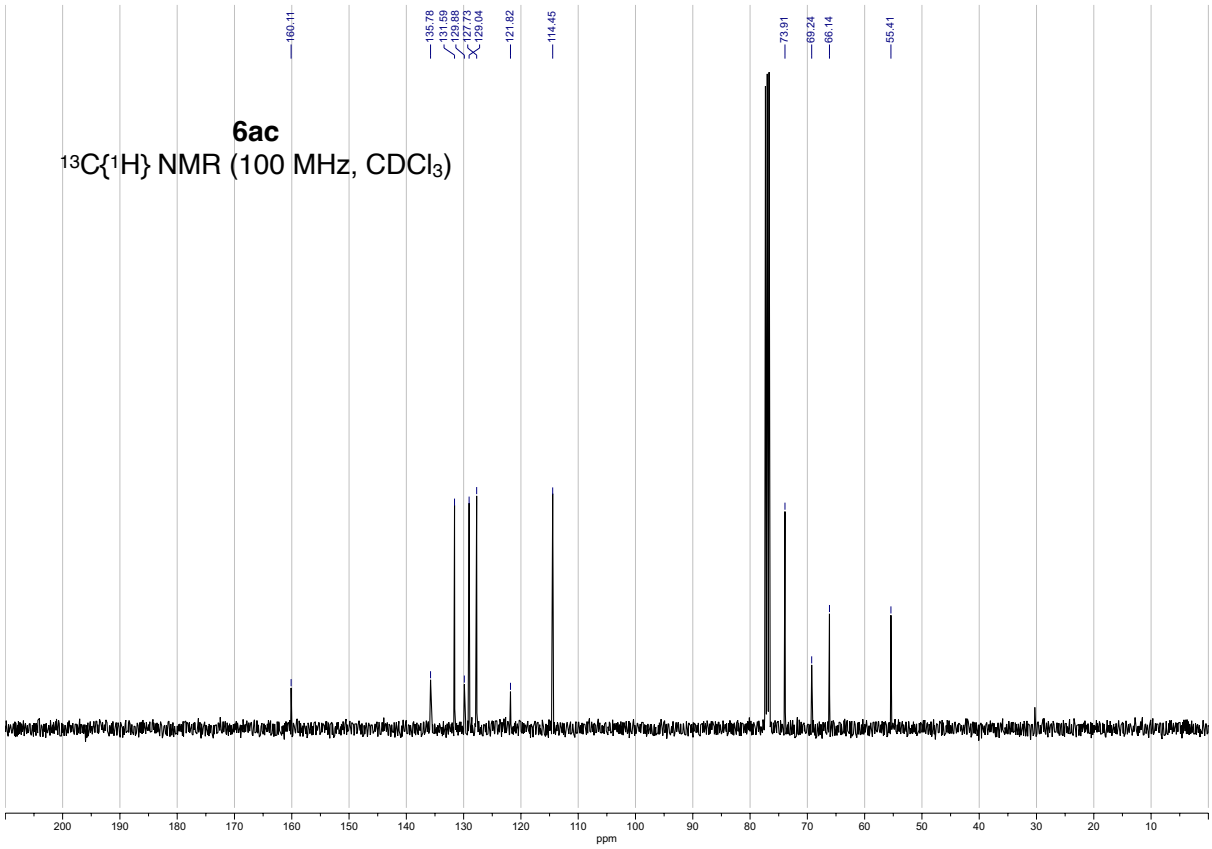
^{1}H NMR (400 MHz, $CDCl_3$)

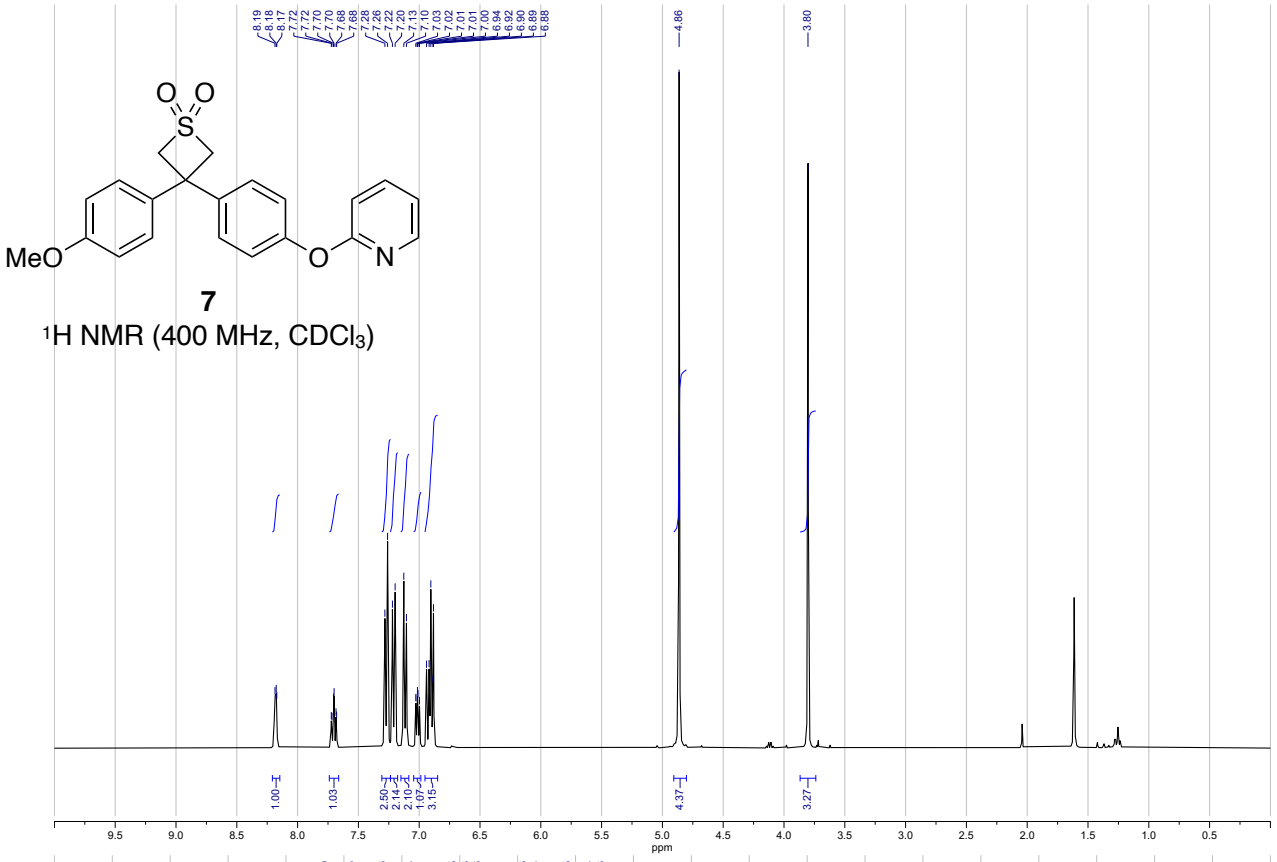


6ab

$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$)

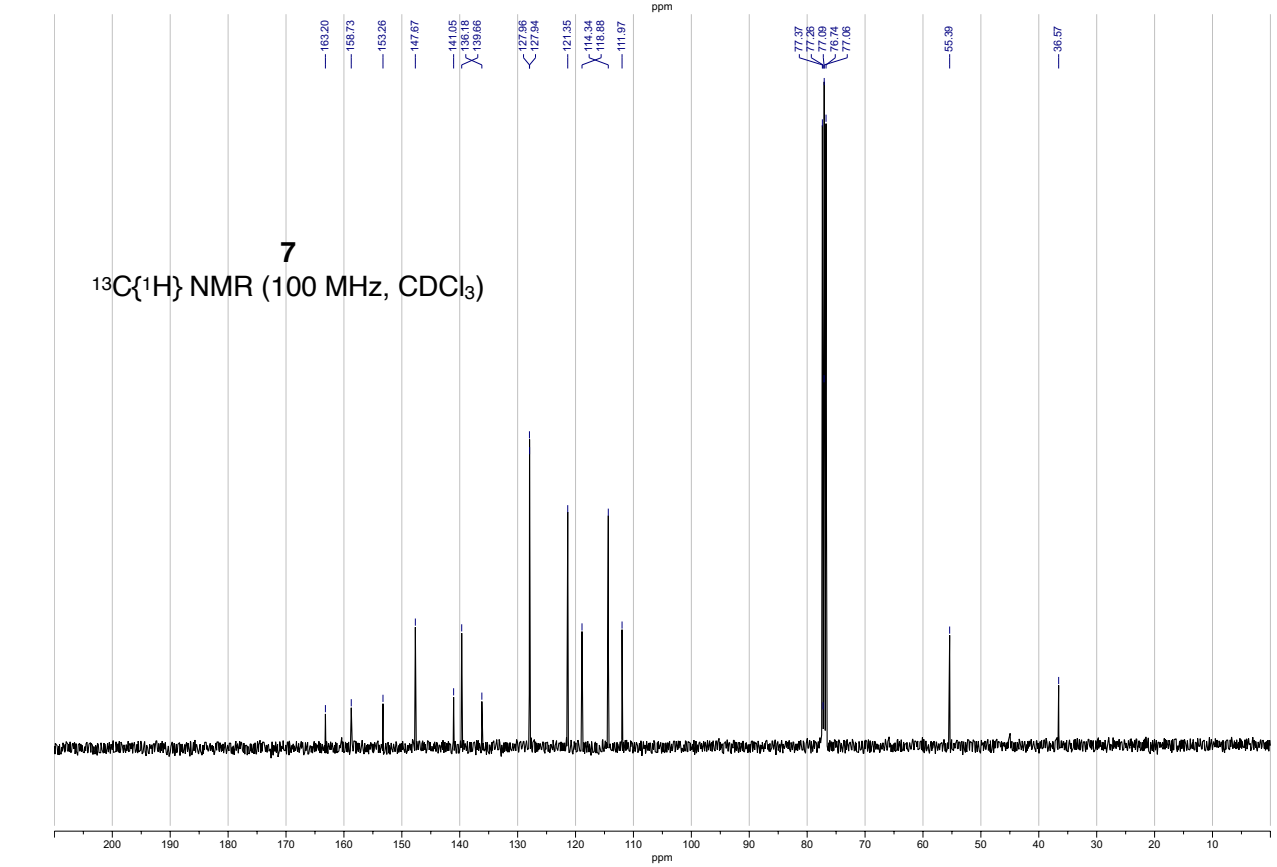

MeO
Br
6ac
^{1}H NMR (400 MHz, $CDCl_3$)
7.46
7.44
7.33
7.31
7.15
7.13
6.98
6.95
4.58
4.54
4.51
4.11
3.85
0.99
1.01
0.99
1.03
2.08
1.04
1.55
ppm


6ac
$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$)
160.11
135.78
131.59
129.88
127.73
129.04
121.82
114.45
73.91
69.24
66.14
55.41
ppm



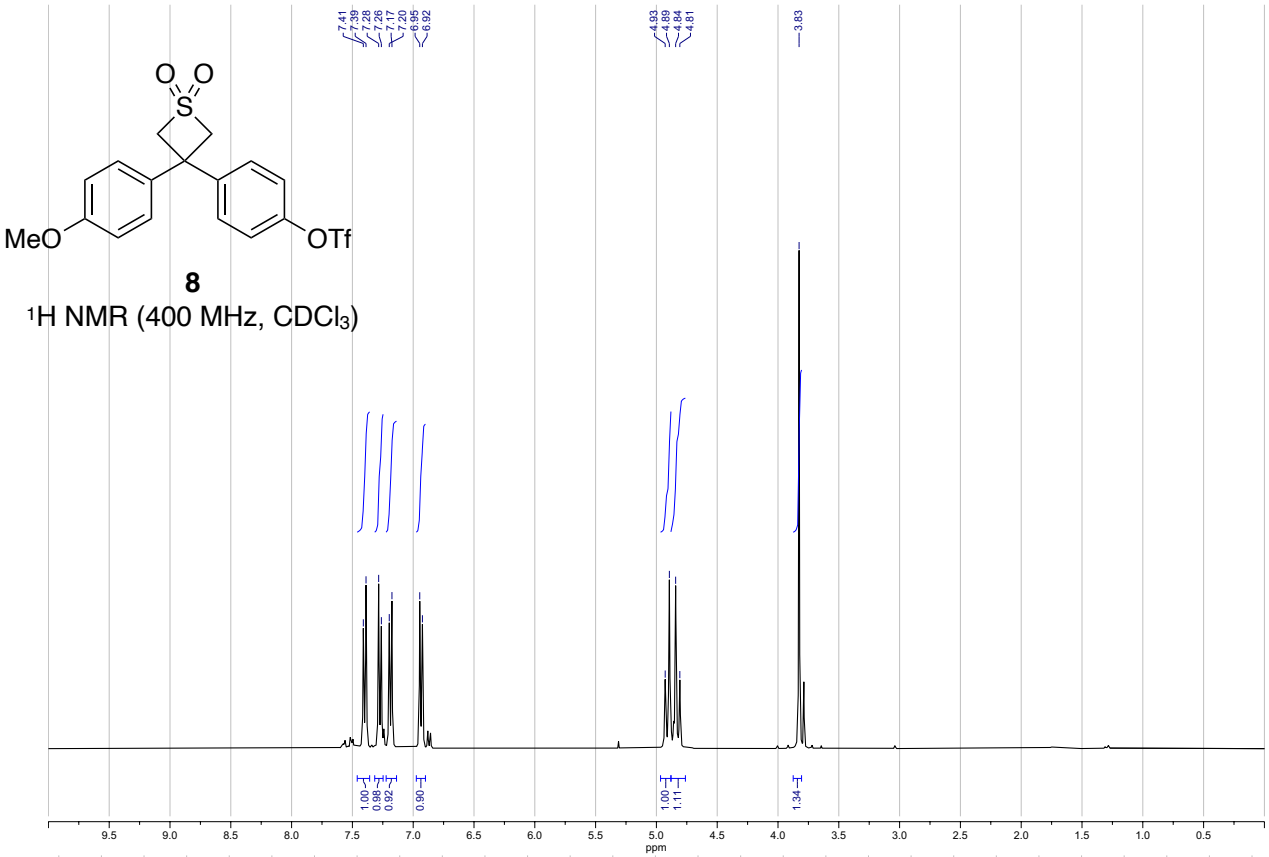
7

^{1}H NMR (400 MHz, $CDCl_3$)



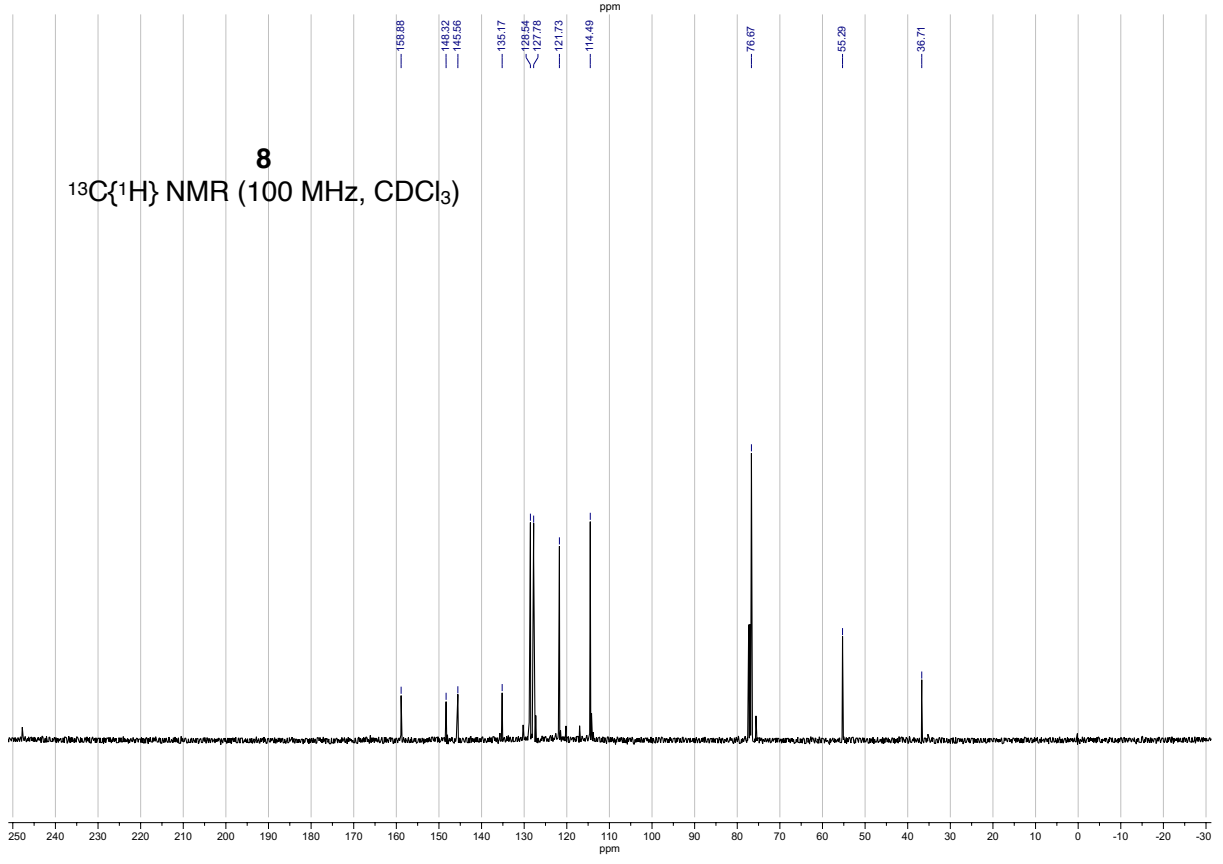
7

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)



8

^{1}H NMR (400 MHz, $CDCl_3$)

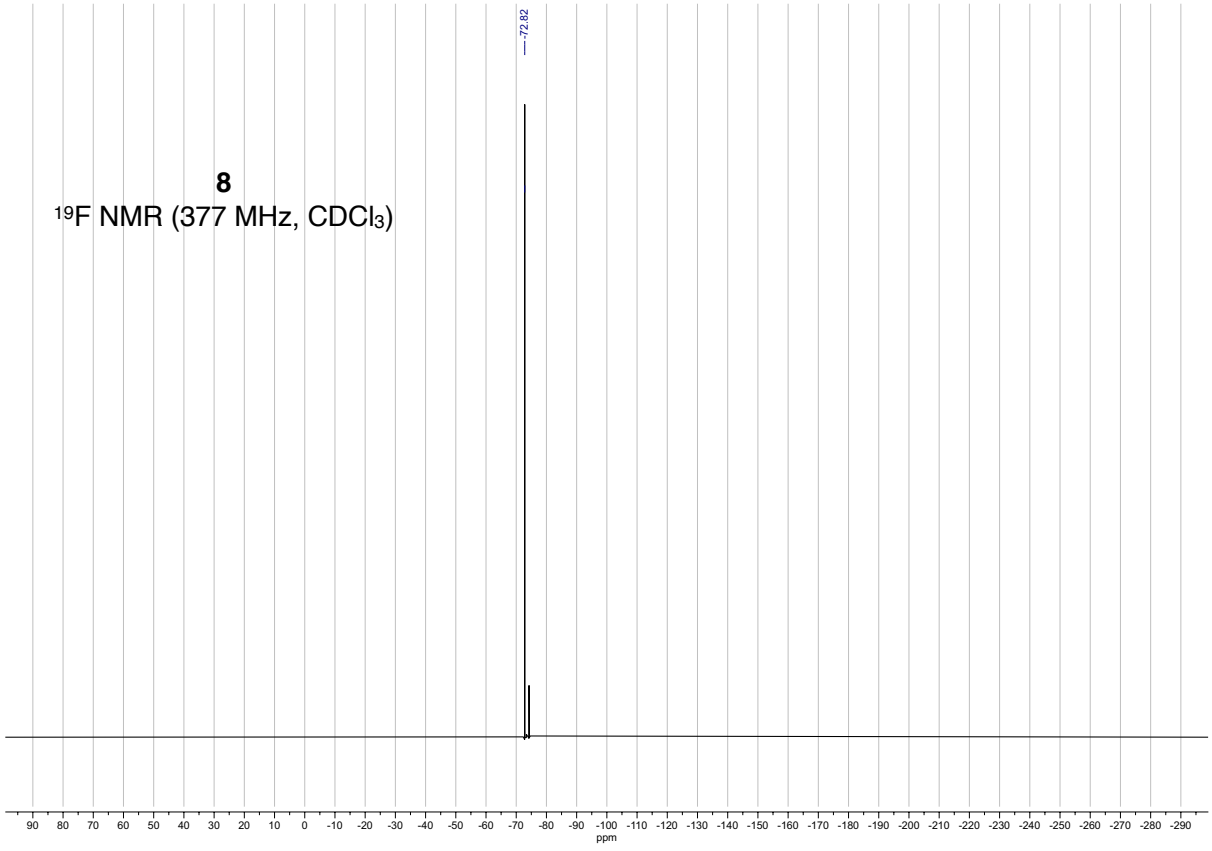


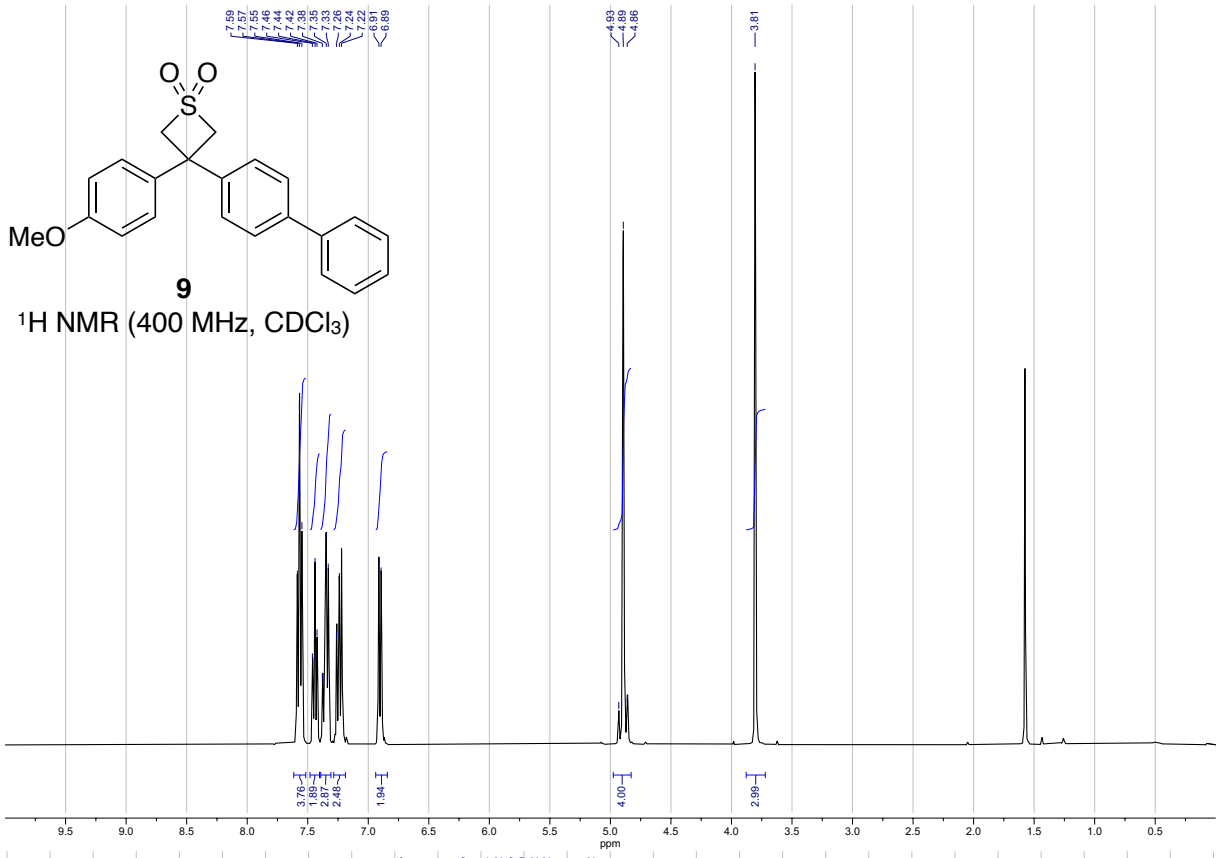
8

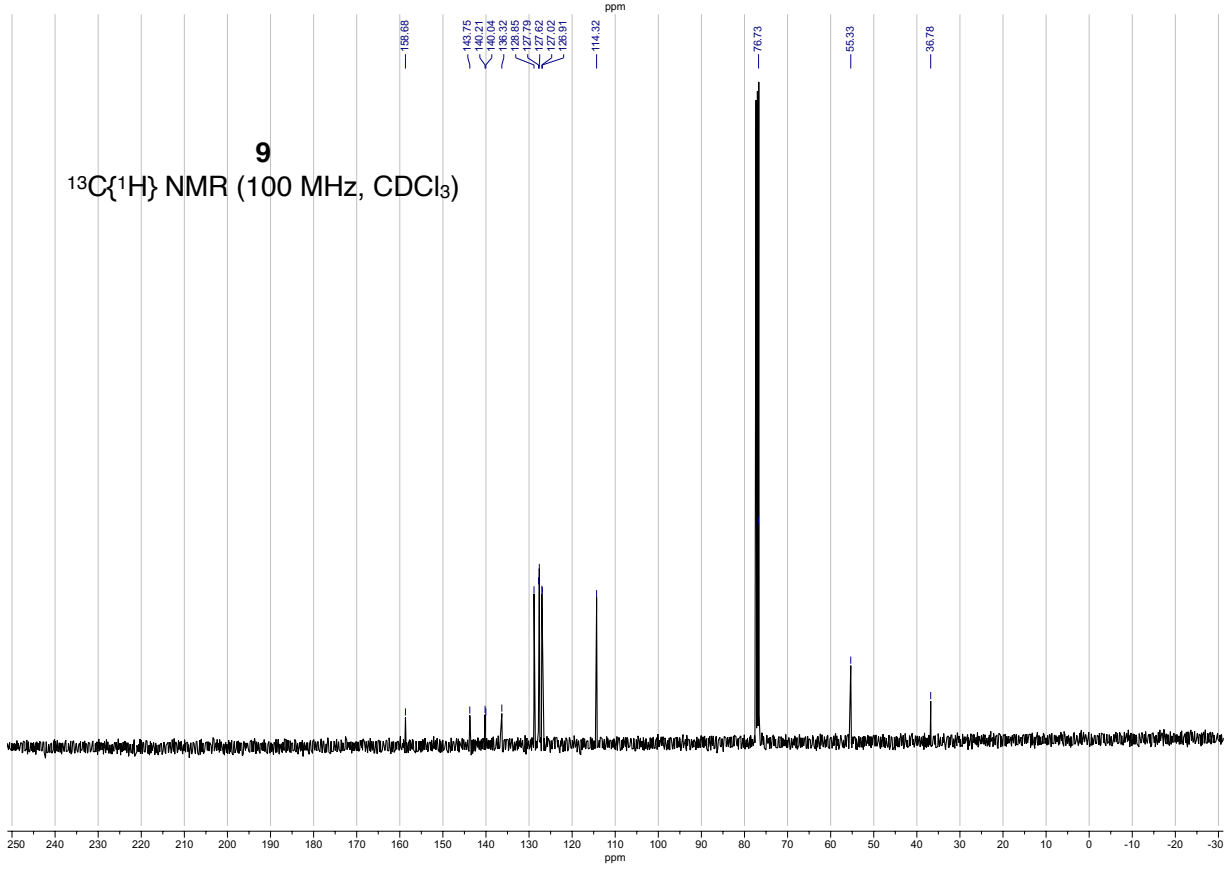
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)

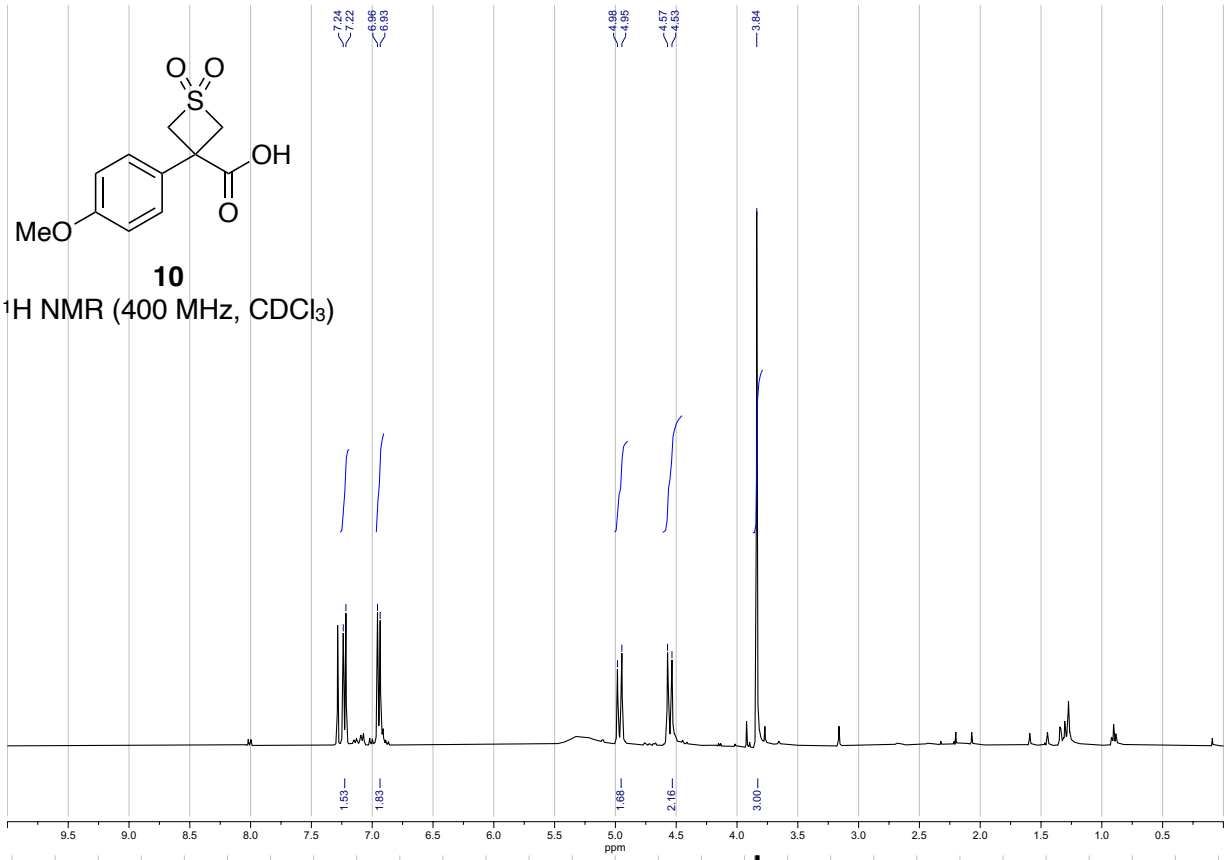
8

^{19}F NMR (377 MHz, $CDCl_3$)



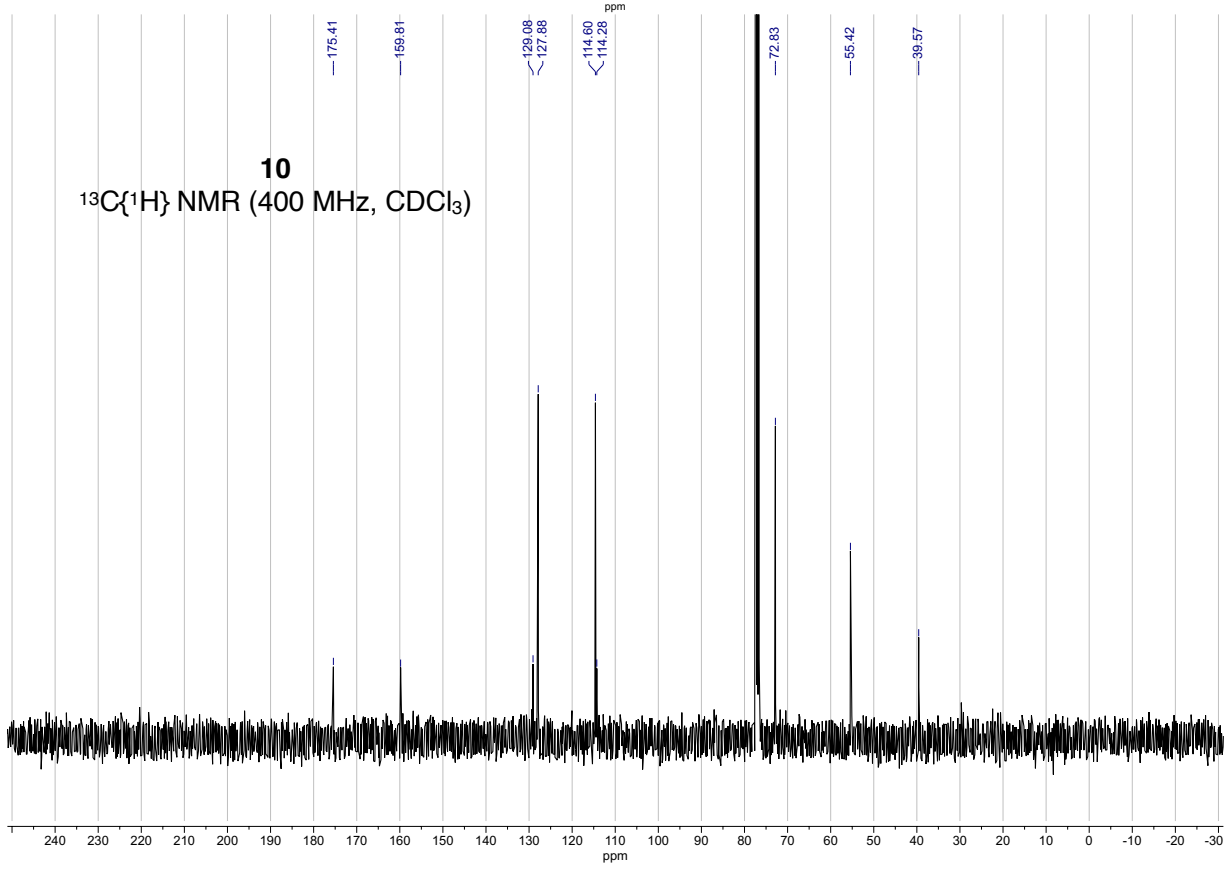

MeO
O
O
S
9
^{1}H NMR (400 MHz, CDCl$_3$)
7.59
7.57
7.55
7.46
7.44
7.42
7.38
7.35
7.33
7.26
7.24
7.22
6.91
6.89
4.93
4.89
4.86
3.81
3.76
3.64
2.87
2.48
1.94
4.00
2.99
ppm


9
^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$)
158.68
143.75
140.21
140.04
136.32
128.85
127.79
127.62
127.02
126.91
114.32
76.73
55.33
36.78
ppm



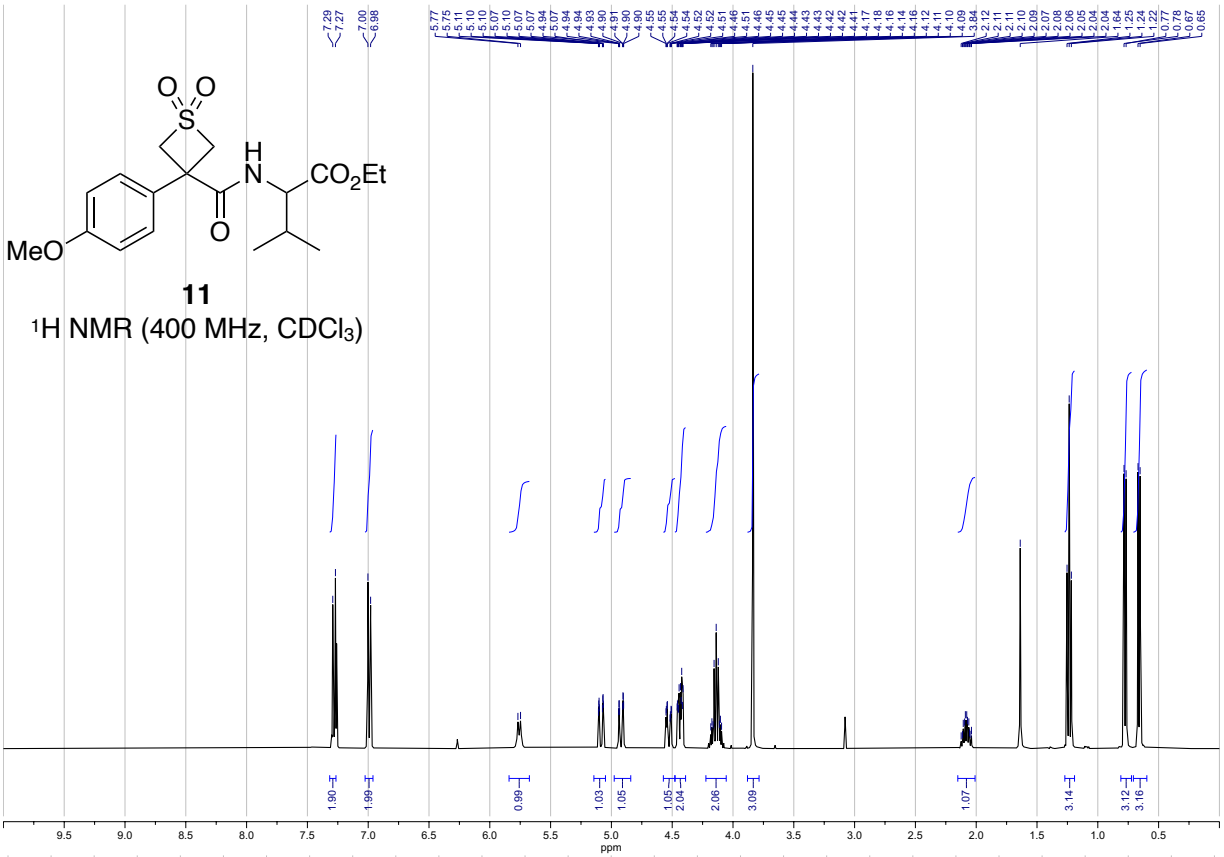
10

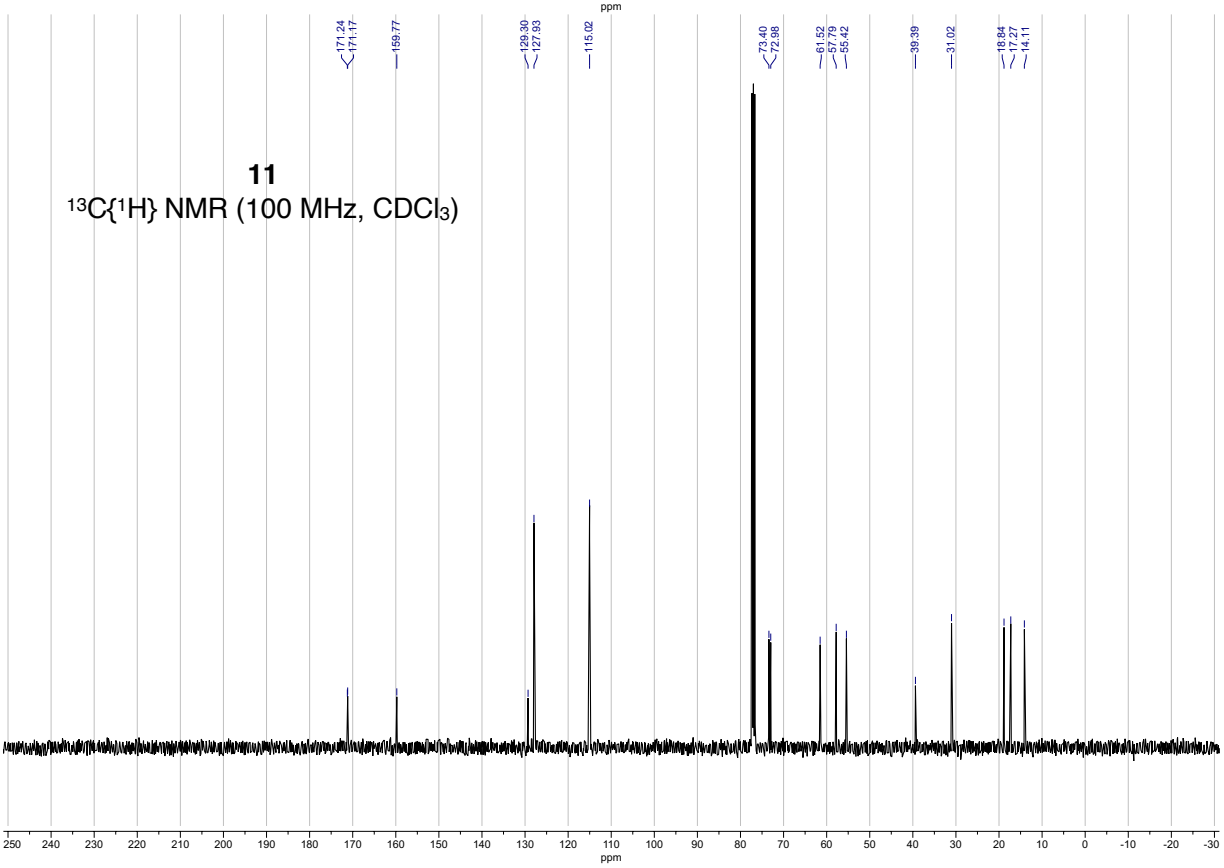
^{1}H NMR (400 MHz, $CDCl_3$)



10

$^{13}C\{^{1}H\}$ NMR (400 MHz, $CDCl_3$)


MeO
O
O
S
H
N
CO2Et
O
11
1H NMR (400 MHz, CDCl3)
ppm


11
13C{1H} NMR (100 MHz, CDCl3)
ppm

References

(1) Dolomanov, O. V.; Bourhis, L. J.; Howard, J. A. K; Puschmann, H. OLEX2:a Complete Structure Solution, Refinement and Analysis Program. *J. Appl. Cryst.* **2009***, 42*, 339–341.
(2) SHELXTL v5.1, Bruker AXS, Madison, *WI*, **1998.**
(3) SHELX-2013, G.M. Sheldrick, *Acta Cryst.*, **2015**, *C71*, 3–8.