Supplementary Material

SAR Studies on Truxillic Acid Mono Esters as a New Class of Antinociceptive Agents, Targeting Fatty Acid Binding Proteins

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Table of Contents

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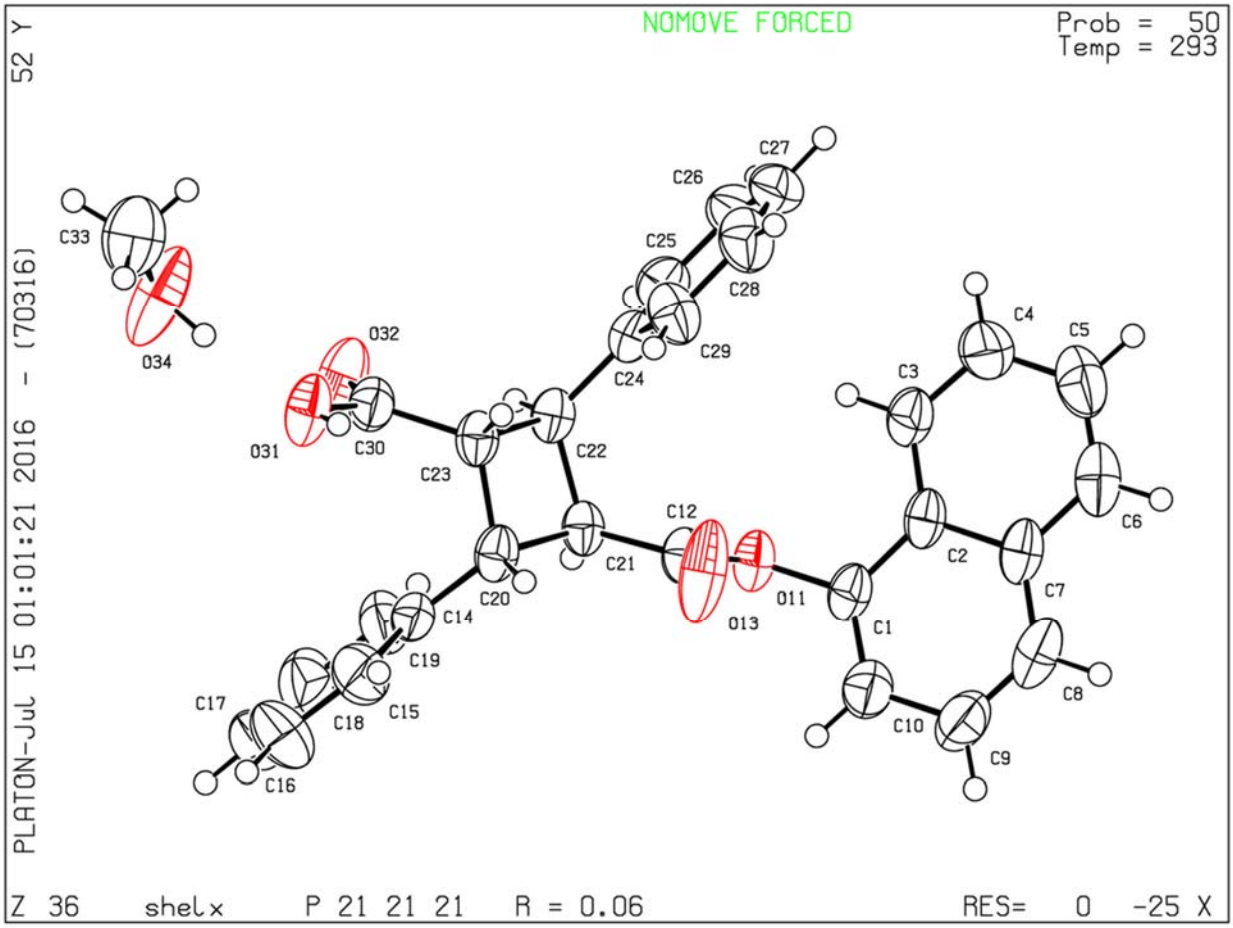


Figure S1. ORTEP representation of the crystal structure of (*R*,*R*,*R*,*R*)-SB-FI-26 (**3-A**)

Table S1. Crystal data and structure refinement for (*R,R,R,R*)-SB-FI-26 (**3-A**).

Identification code	SB-FI-26 A
Empirical formula	$C_{30}H_{28}O_4$
Formula weight	452.52
Temperature/K	293(2)
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a/Å	5.9061(2)
b/Å	8.3860(5)
c/Å	47.6746(19)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	2361.25(19)
Z	4
ρ_{calc}g/cm^3	1.273
μ/mm^{-1}	0.666
F(000)	960.0
Crystal size/mm^3	? × ? × ?
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	7.418 to 146.328
Index ranges	$-5 \leq h \leq 7$, $-10 \leq k \leq 9$, $-56 \leq l \leq 58$
Reflections collected	6076
Independent reflections	3943 [R_{int} = 0.0396, R_{sigma} = 0.0392]
Data/restraints/parameters	3943/0/313
Goodness-of-fit on F^2	1.187
Final R indexes [I>=2σ (I)]	R_1 = 0.0607, wR_2 = 0.1537
Final R indexes [all data]	R_1 = 0.0696, wR_2 = 0.1602
Largest diff. peak/hole / e Å^{-3}	0.24/-0.31
Flack parameter	0.0(3)

Table S2 Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 \times 10^3$) for (*R*,*R*,*R*,*R*)-SB-FI-26 (**3-A**). U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor.

Atom	*x*	*y*	*z*	U(eq)
O11	12254(5)	12069(4)	10822.0(6)	48(3)
O32	6516(6)	13212(6)	11852.7(7)	68(3)
O31	9195(6)	13183(7)	12166.5(6)	65(3)
C1	14134(8)	12124(7)	10639.8(9)	47(3)
C2	14554(9)	13568(7)	10496.0(9)	46(3)
C21	10659(8)	11975(6)	11277.0(8)	40(3)
C12	12743(8)	12153(6)	11101.5(9)	45(3)
O13	14593(6)	12340(8)	11181.5(7)	93(3)
C23	10335(8)	13231(6)	11680.6(9)	43(3)
C20	11226(8)	11549(6)	11588.6(9)	45(3)
C22	9477(8)	13545(6)	11378.6(9)	41(3)
C30	8497(10)	13225(6)	11902.5(10)	49(3)
C6	16953(12)	15040(9)	10169.0(11)	69(3)
C7	16485(10)	13611(7)	10314.2(9)	53(3)
C14	10133(9)	10100(6)	11711.8(10)	48(3)
C25	8385(9)	15690(7)	11043.3(11)	51(3)
O34	3414(8)	13546(9)	12264.3(9)	108(4)
C24	9950(8)	15101(6)	11234.2(9)	43(3)
C3	13206(10)	14936(7)	10522(1)	54(3)
C29	11881(11)	15991(7)	11280.9(11)	59(3)
C8	17823(10)	12231(9)	10284.0(11)	69(3)
C4	13709(13)	16290(8)	10374.9(11)	69(3)
C27	10647(11)	17972(7)	10952.4(11)	64(3)
C10	15433(11)	10812(8)	10603.4(11)	61(3)
C9	17296(12)	10858(9)	10421.4(12)	72(3)
C5	15601(13)	16338(9)	10197.4(12)	76(4)
C15	11248(14)	9305(8)	11927.1(13)	78(3)
C26	8746(11)	17099(7)	10902.3(11)	63(3)
C19	8089(12)	9502(7)	11624.8(12)	66(3)
C28	12242(12)	17425(7)	11141.7(11)	66(3)
C18	7165(14)	8156(8)	11746.2(14)	84(4)
C16	10300(20)	7960(11)	12049.1(17)	112(4)
C17	8320(20)	7383(9)	11957.4(17)	105(4)
C33	4125(14)	14668(11)	12463.7(14)	95(4)

Table S3. Anisotropic Displacement Parameters ($Å^2 \times 10^3$) for (*R*,*R*,*R*,*R*)-SB-FI-26 (**3-A**). The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\ldots]$.

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O11	41(3)	72(4)	32(3)	2.3(15)	3.7(13)	-3.0(19)
O32	40(3)	109(4)	54(4)	-13(2)	7.3(17)	-12(2)
O31	53(4)	103(4)	37(3)	-1(2)	6.6(16)	-3(3)
C1	42(4)	67(4)	32(4)	-1(2)	1.8(19)	2(3)
C2	42(4)	68(4)	27(3)	-1(2)	0.4(19)	-5(3)
C21	36(4)	50(4)	35(4)	-1(2)	0.2(19)	-13(2)
C12	45(4)	55(4)	35(4)	-3(2)	3(2)	-10(3)
O13	43(4)	196(7)	41(3)	-10(3)	2.0(17)	-41(3)
C23	40(4)	54(4)	34(4)	-2(2)	0.8(19)	-10(2)
C20	36(4)	64(4)	35(4)	2(2)	-0.1(19)	-1(3)
C22	31(4)	55(4)	37(4)	-2(2)	-0.8(18)	-7(2)
C30	55(4)	50(4)	42(4)	-5(2)	9(2)	-9(3)
C6	68(5)	94(6)	44(4)	4(3)	10(3)	-19(4)
C7	45(4)	81(5)	33(4)	-2(2)	3(2)	-8(3)
C14	56(4)	52(4)	38(4)	4(2)	11(2)	10(3)
C25	36(4)	60(4)	58(4)	-1(2)	0(2)	3(3)
O34	47(4)	214(8)	63(4)	-41(4)	9(2)	-2(4)
C24	36(4)	53(4)	40(4)	-3(2)	4(2)	-1(2)
C3	54(4)	69(4)	37(4)	1(2)	4(2)	2(3)
C29	70(5)	60(4)	47(4)	4(2)	-5(3)	-18(3)
C8	51(4)	110(6)	45(4)	-7(3)	11(2)	9(4)
C4	90(5)	66(5)	51(4)	7(3)	4(3)	9(4)
C27	93(5)	40(4)	58(4)	2(2)	12(3)	2(3)
C10	64(5)	69(5)	51(4)	4(3)	10(3)	7(3)
C9	69(5)	88(5)	58(4)	-1(3)	15(3)	25(4)
C5	97(6)	82(5)	50(4)	11(3)	6(3)	-20(4)
C15	90(6)	81(5)	61(4)	24(3)	4(4)	23(4)
C26	72(5)	57(4)	60(4)	7(3)	-2(3)	12(3)
C19	75(5)	66(5)	57(4)	7(3)	12(3)	-15(4)
C28	78(5)	61(4)	60(4)	-6(3)	5(3)	-26(3)
C18	99(6)	72(5)	82(5)	-6(4)	31(4)	-24(4)
C16	164(10)	91(7)	81(6)	46(5)	17(6)	31(7)
C17	171(10)	55(5)	89(6)	13(4)	55(6)	2(6)
C33	98(7)	122(7)	65(5)	-4(4)	2(4)	-7(6)

Table S4. Bond Lengths for (*R*,*R*,*R*,*R*)-SB-FI-26 (**3-A**).

Atom	Atom	Length/Å	Atom	Atom	Length/Å
O11	C12	1.365(5)	C7	C8	1.409(8)
O11	C1	1.410(5)	C14	C19	1.371(9)
O32	C30	1.194(7)	C14	C15	1.390(8)
O31	C30	1.325(6)	C25	C26	1.376(8)
C1	C10	1.352(8)	C25	C24	1.388(7)
C1	C2	1.413(7)	O34	C33	1.402(9)
C2	C3	1.402(7)	C24	C29	1.381(8)
C2	C7	1.433(7)	C3	C4	1.367(8)
C21	C12	1.496(6)	C29	C28	1.390(7)
C21	C20	1.564(6)	C8	C9	1.361(9)
C21	C22	1.567(7)	C4	C5	1.402(9)
C12	O13	1.168(6)	C27	C26	1.362(9)
C23	C30	1.516(6)	C27	C28	1.383(8)
C23	C22	1.549(6)	C10	C9	1.402(8)
C23	C20	1.568(7)	C15	C16	1.387(11)
C20	C14	1.496(7)	C19	C18	1.381(8)
C22	C24	1.502(7)	C18	C17	1.379(11)
C6	C5	1.357(9)	C16	C17	1.339(13)
C6	C7	1.411(8)			

Table S5. Bond Angles for (*R*,*R*,*R*,*R*)-SB-FI-26 (**3-A**).

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
C12	O11	C1	115.6(4)	C8	C7	C6	122.5(5)
C10	C1	O11	119.9(5)	C8	C7	C2	119.2(5)
C10	C1	C2	122.3(5)	C6	C7	C2	118.3(6)
O11	C1	C2	117.7(5)	C19	C14	C15	117.7(6)
C3	C2	C1	123.9(4)	C19	C14	C20	123.9(5)
C3	C2	C7	119.0(5)	C15	C14	C20	118.4(6)
C1	C2	C7	117.1(5)	C26	C25	C24	121.5(6)
C12	C21	C20	112.2(4)	C29	C24	C25	117.6(5)
C12	C21	C22	117.1(4)	C29	C24	C22	123.3(5)
C20	C21	C22	89.6(3)	C25	C24	C22	119.1(5)
O13	C12	O11	121.6(4)	C4	C3	C2	120.7(5)
O13	C12	C21	126.9(4)	C24	C29	C28	121.1(6)
O11	C12	C21	111.5(4)	C9	C8	C7	121.2(5)
C30	C23	C22	114.5(4)	C3	C4	C5	120.5(6)
C30	C23	C20	115.6(4)	C26	C27	C28	119.8(5)
C22	C23	C20	90.1(3)	C1	C10	C9	120.2(6)
C14	C20	C21	117.8(4)	C8	C9	C10	120.0(6)
C14	C20	C23	118.4(4)	C6	C5	C4	120.4(6)
C21	C20	C23	89.3(4)	C16	C15	C14	120.6(8)
C24	C22	C23	120.9(4)	C27	C26	C25	120.3(6)
C24	C22	C21	120.4(4)	C14	C19	C18	121.4(7)
C23	C22	C21	89.9(4)	C27	C28	C29	119.6(6)
O32	C30	O31	119.6(5)	C17	C18	C19	119.6(8)
O32	C30	C23	124.3(5)	C17	C16	C15	120.6(8)
O31	C30	C23	116.1(5)	C16	C17	C18	120.1(8)
C5	C6	C7	121.1(6)				

Table S6. Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for (*R*,*R*,*R*,*R*)-SB-FI-26 (**3-A**).

Atom	*x*	*y*	*z*	U(eq)
H31	10571	13307	12172	97
H21	9578	11223	11194	49
H23	11581	13949	11731	51
H20	12870	11494	11614	54
H22	7837	13368	11376	49
H6	18210	15093	10052	82
H25	7062	15119	11010	61
H3	11955	14922	10641	64
H29	12958	15624	11408	71
H8	19090	12258	10168	82
H4	12791	17185	10393	82
H27	10873	18935	10860	77
H10	15089	9878	10699	74
H9	18172	9949	10395	86
H5	15931	17265	10098	92
H15	12642	9678	11990	93
H26	7688	17457	10772	75
H19	7310	10013	11481	79
H28	13548	18013	11176	80
H18	5770	7773	11686	101
H16	11050	7454	12196	134
H17	7728	6459	12036	126
H33A	2903	14894	12590	142
H33B	4574	15632	12370	142
H33C	5386	14247	12567	142
H1	4600(70)	13230(50)	12182(7)	10(3)

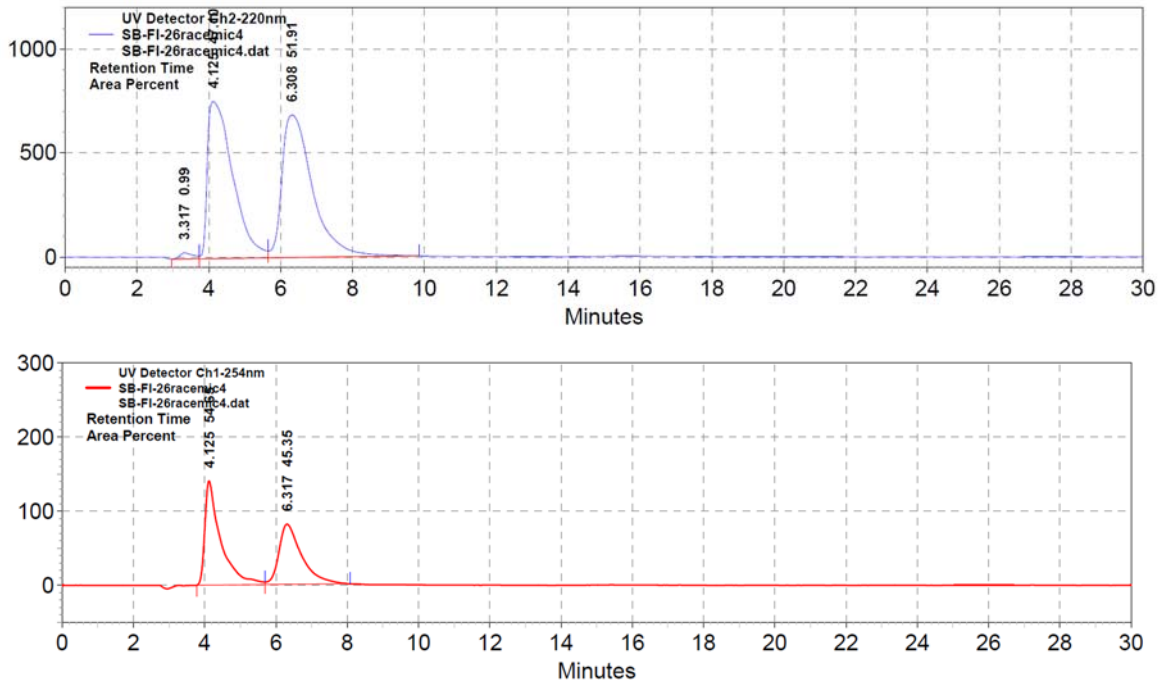


Figure S2. Separation of two enantiomers of SB-FI-26 using racemic SB-FI-26 (65%: 35% isopropanol: hexanes Chiralcel ODH).

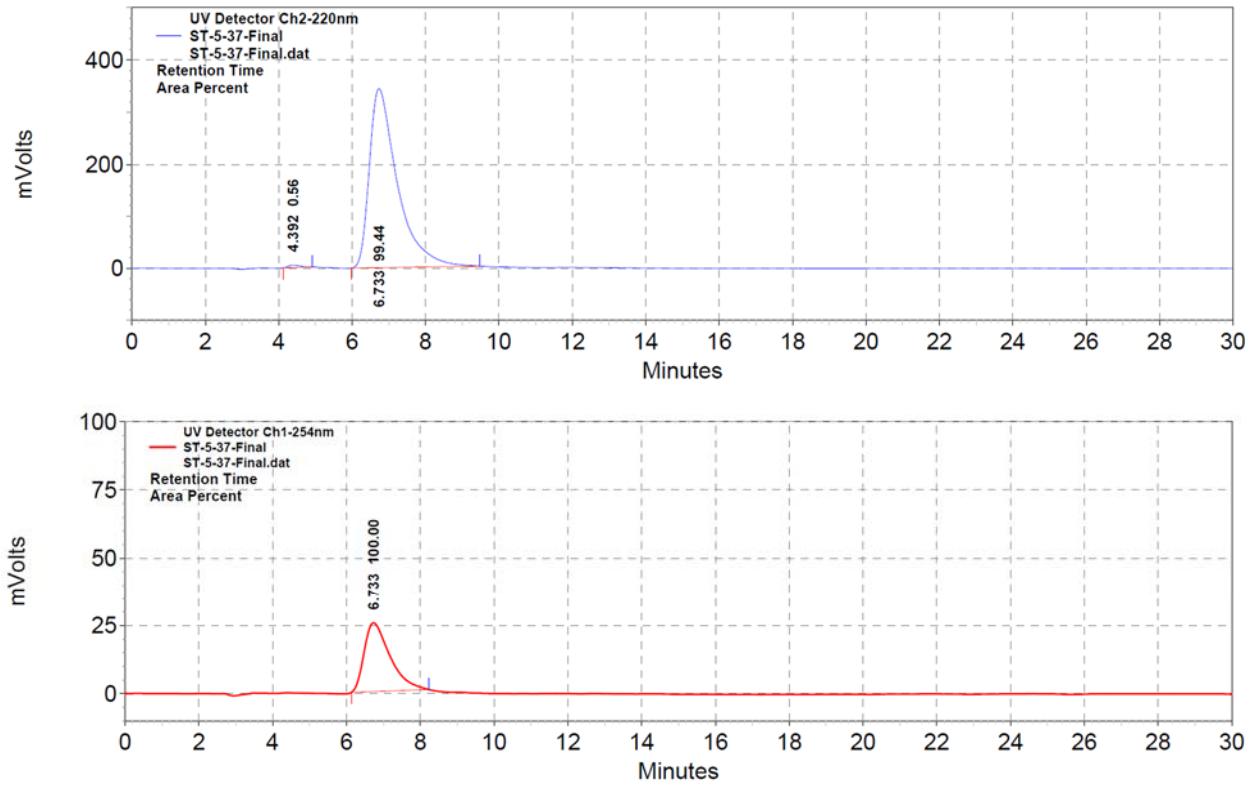


Figure S3. Optical resolution of *rac*-SB-FI-26 with L-phenylalaninol, giving SB-FI-26A (**3-A**), i.e., (*R*,*R*,*R*,*R*)-SB-FI-26 (65%: 35% isopropanol: hexanes Chiralcel ODH).

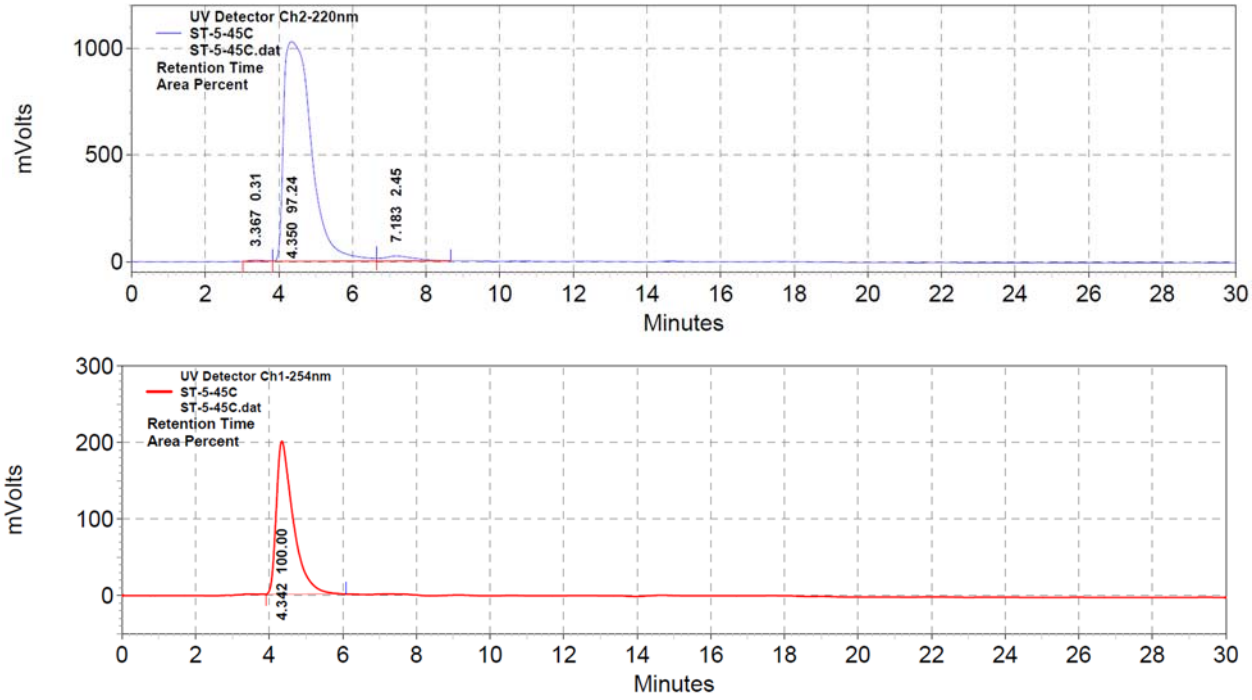
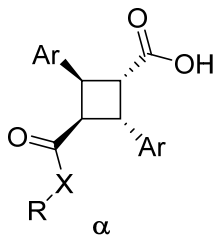
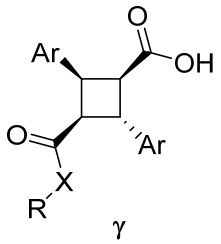


Figure S4. Optical resolution *rac*-SB-FI-26 with D-phenylalaninol, giving SB-FI-26B (**3-B**), i.e., (*S*,*S*,*S*,*S*)-SB-FI-26 (65%: 35% isopropanol: hexanes Chiralcel ODH).

Table S7. Docking energy scores and cLogP values of **3**-analogs for FABP5 and FABP7



α



γ

Compound*	Ar	X	R	FABP5 (kcal/mol)	FABP7 (kcal/mol)	cLogP	Selected for synthesis
(R,R,R,R)-**3**	Ph	O	1-naphthyl	-7.95	-9.46	6.97	✓
(S,S,S,S)-**3**	Ph	O	1-naphthyl	-8.17	-9.49	6.97	✓
3a	Ph	O	benzyl	-8.14	-8.77	5.28	✓
3b	Ph	O	4-MeO-benzyl	-7.60	-8.92	5.20	✓
3c	Ph	O	4-F-benzyl	-7.86	-7.79	5.42	✓
3d	Ph	O	4-Br-benzyl	-8.40	-8.27	6.13	✓
3e	Ph	O	2-iodophenyl	-8.15	-9.98	5.77	✓
3f	Ph	O	3-ethynylphenyl	-7.39	-8.88	5.06	✓
3g	Ph	O	biphenyl-2-yl	-8.75	-9.94	6.12	✓
3h	Ph	O	biphenyl-3-yl	-7.63	-8.91	6.68	✓
3i	Ph	O	biphenyl-4-yl	-8.21	-8.13	6.68	✓
3j	Ph	O	2'-HO-biphenyl-2-yl	-8.06	-9.24	5.19	✓
3k	Ph	O	2,4,5-trichlorophenyl	-8.44	-9.10	6.67	✓
3l-a (*R,R,R,R*)	Ph	O	(1*R*,2*S*)-2-phenylcyclohex-1-yl	-8.86	-10.25	7.17	✓
3l-b (*S,S,S,S*)	Ph	O	(1*S*,2*R*)-2-phenylcyclohex-1-yl	-8.40	-10.20	7.17	✓
3l-c (*S,S,S,S*)	Ph	O	(1*R*,2*S*)-2-phenylcyclohex-1-yl	-8.53	-10.56	7.17	✓
3l-d (*R,R,R,R*)	Ph	O	(1*S*,2*R*)-2-phenylcyclohex-1-yl	-8.70	-10.48	7.17	✓
3m	Ph	O	Indan-2-yl	-9.27	-8.63	5.56	✓
3n	Ph	O	CF_3CH_2-	-6.36	-7.20	3.87	✓
3o	Ph	O	6-acetamidonaphth-1-yl	-8.92	-10.08	5.10	✓
3p	Ph	O	5-ethynylnaphth-1-yl	-7.63	-9.21	6.23	✓
3q	Ph	O	9-fluorenylmethyl	-8.53	-10.77	7.10	✓
3r	Ph	O	cyclohexyl	-6.47	-9.30	5.61	✓

3s	Ph	O	3-[1-(3,6,9-trioxa-dodecanyl)-1,2,3-triazol-4-yl]phenyl	-5.47	-8.94	4.49	✓
3o-γ	Ph	O	6-acetamidonaphth-1-yl	-7.69	-8.94	5.10	✓
4a	3-MeO-4-HO-Ph	O	1-naphthyl	-7.04	-8.05	4.33	✓
4b	2-MeO-Ph	O	1-naphthyl	-8.59	-8.90	5.00	✓
4c	2-O_2N-Ph	O	1-naphthyl	-9.37	-10.75	5.29	✓
4d	4-HO-Ph	O	1-naphthyl	-8.14	-9.23	4.63	✓
4e	2-MeO-Ph	O	(1*R*,2*S*)-2-phenylcyclohex-1-yl	-7.99	-9.29	6.20	✓
4f	2-Cl-Ph	O	(1*R*,2*S*)-2-phenylcyclohex-1-yl	-8.37	-11.22	8.59	✓
4g	2,6-Cl_2-Ph	O	(1*R*,2*S*)-2-phenylcyclohex-1-yl	-8.49	-11.87	10.01	✓
4h	2-Br-Ph	O	(1*R*,2*S*)-2-phenylcyclohex-1-yl	-9.09	-10.45	8.89	✓
4i	2-O_2N-Ph	O	(1*R*,2*S*)-2-phenylcyclohex-1-yl	-10.01	-10.57	6.49	✓
4j	2-MeO-Ph	O	9-fluorenylmethyl	-8.41	-9.77	6.14	✓
4k	2-Cl-Ph	O	9-fluorenylmethyl	-8.76	-11.09	8.52	✓
4l	2-MeO-Ph	O	quinolin-5-yl	-8.42	-9.10	4.89	✓
5a	Ph	O	benzyl	-6.85	-8.55	7.50	✓
5b	Ph	O	4-MeO-benzyl	-7.09	-8.00	7.33	✓
5c	Ph	O	4-F-benzyl	-7.13	-8.30	7.78	✓
5d	Ph	O	tetrahydropyran-4-ylmethyl	-6.85	-8.83	3.97	✓
5e	Ph	O	biphenyl-3-yl	-8.47	-10.14	10.29	✓
6a	Ph	NH	4-(5,6,7,8-tetrahydronaphth-2-yl)thiazol-2-yl	-9.60	N.D.**	7.48	✓
6b	Ph	NH	biphenyl-4-yl	-6.32	-8.36	6.46	✓
6a-γ	Ph	NH	4-(5,6,7,8-tetrahydronaphth-2-yl)thiazol-2-yl	-8.05	N.D.**	7.48	✓
	Ph	O	2-(trifluoromethyl)phenyl	-6.89	-8.01	5.92	
	Ph	O	6,7-dihydro-5H-cyclopenta[d]pyridazin-6-yl	-6.71	-8.48	2.83	
	Ph	O	5-((trifluoromethoxy)methyl) naphthalen-1-yl	-6.85	-7.86	6.73	
	Ph	NH	4-cyanophenyl	-6.43	-7.62	4.61	
	Ph	O	2,4-dimethoxylphenly	-6.15	-7.15	4.52	
	4-O_2N-Ph	O	3-chloropyridin-4-yl	-6.03	-6.78	3.72	
	2-NH_2-Ph	O	quinolin-5-yl	-6.44	-7.48	2.30	

4-O_2N-Ph	O	quinolin-5-yl	-6.23	-7.08	4.46

***1x:** unsubstituted and substituted α-truxillic acid; **3x:** α-truxillic acid mono ester; **3o-γ:** γ-truxillic acid mono ester; **4x:** substitutedγ-truxillic acid mono ester; **5x**: α-truxillic acid mono ester; **6x**: α-truxillic acid mono amide; **6a-γ,** γ-truxillic acid mono amide). **The compound does not fit into the binding pocket.

Protein Expression and Purification of FABP3

pET28a vector consisting of human FABP3 gene was expressed in BL21(DE3) strain. Cells were grown at 37 °C to OD_{600} = 0.5-0.6 before being induced with 0.5 mM IPTG and were expressed at 16 °C for 16 hours. Cells were harvested by centrifugation and were lysed by passing through a Microfluidizer cell disruptor in 10 mM potassium phosphate (pH 8.0), 10 mM imidazole, and 0.25 M NaCl. The homogenate was clarified by spinning at 27,000g, and the supernatant was applied to a HiTrap-Ni column (GE Healthcare) pre-equilibrated with the lysis buffer. His-tagged FABP3 was eluted with a 10–300 mM imidazole gradient in 10mM potassium phosphate (pH 8.0) and 0.25 M NaCl. To remove the N-termianl His-tag, FABP3 was incubated with thrombin overnight at 4 °C in 50 mM Tris (pH 8.5) and 0.15 M NaCl. After clearing the undigested His-FABPs by passing through HiTrap-Ni column, FABP3 was applied to a Superdex 75 column (16 x 1000 mm, GE Healthcare) equilibrated with 10mM Tris (pH 8.5), 1 mM dithiothreitol, and 0.15 M NaCl. Delipidation was performed by incubating FABP3 with hydroxyalkoxypropyl-dextran (Sigma) for 1 hour at 37 °C. The purified FABP3 was concentrated to 50 mg/ml for crystallization.

Crystallization and structure determination of FABP3

Before crystallization, FABP3 was incubated with SBFI-26 at room temperature for 30 min at a molar ratio of 1: 2 (protein: ligand). FABP3 crystals were grown at 293 °K by sitting-drop vapor diffusion method using 0.1 M sodium cacodylate pH 7.0, and 2.3 M ammonium sulfate as the mother liquor. Diffraction data to resolution of 1.4Å were collected at Lilly Research Laboratories Collaborative Access Team (LRL-CAT) beamline of Advanced Photon Source (APS), Argonne National Laboratory, and were processed with Mosflm software. The space group of FABP3 crystal was P21 and the structure was solved by molecular replacement program PHASER using previously solved FABP3 structure (PDB ID: 1HMS) as initial search model. However, we only found endogenous palmitic acid from *E. coli* in the ligand binding pocket. Crystallographic data are summarized in Table S7.

Table S8. Data collection and refinement statistics for FABP3

	Human FABP3
Data collection	
Wavelength	0.97931
Space group	P 1 21 1
Cell dimensions	
a, *b*, *c* (Å)	43.50, 52.90, 55.51
α, β, γ (°)	90.00, 97.45, 90.00
Resolution (Å)	20.39 – 1.40 (1.48 - 1.40)*
R_{merge} (%)	6.0 (31.8)
$I / \sigma I$	14.0 (4.4)
Total reflections	203192
Completeness (%)	96.6 (95)
Redundancy	4.3 (4.3)
Refinement	
Resolution (Å)	19.54 – 1.40
No. reflections	47498
R_{work} / R_{free}	0.1702 / 0.1979
No. of non-hydrogen atoms	2634
Protein	2216
Ligand	56
Water	362
B-factors	15.07
Protein	13.29
Ligand/ion	20.97
Water	25.08
R.m.s. deviations	
Bond lengths (Å)	0.005
Bond angles (°)	0.781
Ramachandran statistics (%)	
Favored	99.3
Allowed	0.7
Outliers	0

*Values in parentheses are for highest-resolution shell.

Autodock 4.2 Parameters

Docking (Lamarckian Genetic Algorithm)

```
rmstol 2.0                  # cluster_tolerance/A
extnrg 1000.0               # external grid energy
e0max 0.0 10000             # max initial energy; max number of retries
ga_pop_size 150             # number of individuals in population
ga_num_evals 2500000        # maximum number of energy evaluations
ga_num_generations 27000    # maximum number of generations
ga_elitism 1                # number of top individuals to survive to next generation
ga_mutation_rate 0.02       # rate of gene mutation
ga_crossover_rate 0.8       # rate of crossover
ga_window_size 10           #
ga_cauchy_alpha 0.0         # Alpha parameter of Cauchy distribution
ga_cauchy_beta 1.0          # Beta parameter Cauchy distribution
set_ga                      # set the above parameters for GA or LGA
sw_max_its 300              # iterations of Solis & Wets local search
sw_max_succ 4               # consecutive successes before changing rho
sw_max_fail 4               # consecutive failures before changing rho
sw_rho 1.0                  # size of local search space to sample
sw_lb_rho 0.01              # lower bound on rho
ls_search_freq 0.06         # probability of performing local search on individual
set_psw1                    # set the above pseudo-Solis & Wets parameters
unbound_model bound         # state of unbound ligand
ga_run 10                   # do this many hybrid GA-LS runs
```

Energy Minimization Parameters

```
rmstol 1.0                  # cluster_tolerance/A
extnrg 1000.0               # external grid energy
e0max 0.0 10000             # max initial energy; max number of retries
ga_pop_size 1500            # number of individuals in population
sw_max_its 30000            # iterations of Solis & Wets local search
sw_max_succ 20              # consecutive successes before changing rho
sw_max_fail 20              # consecutive failures before changing rho
sw_rho 1000.0               # size of local search space to sample
sw_lb_rho 0.01              # lower bound on rho
set_psw1                    # set the above pseudo-Solis & Wets parameters
unbound_model bound         # state of unbound ligand
do_local_only 50            # do this many
```

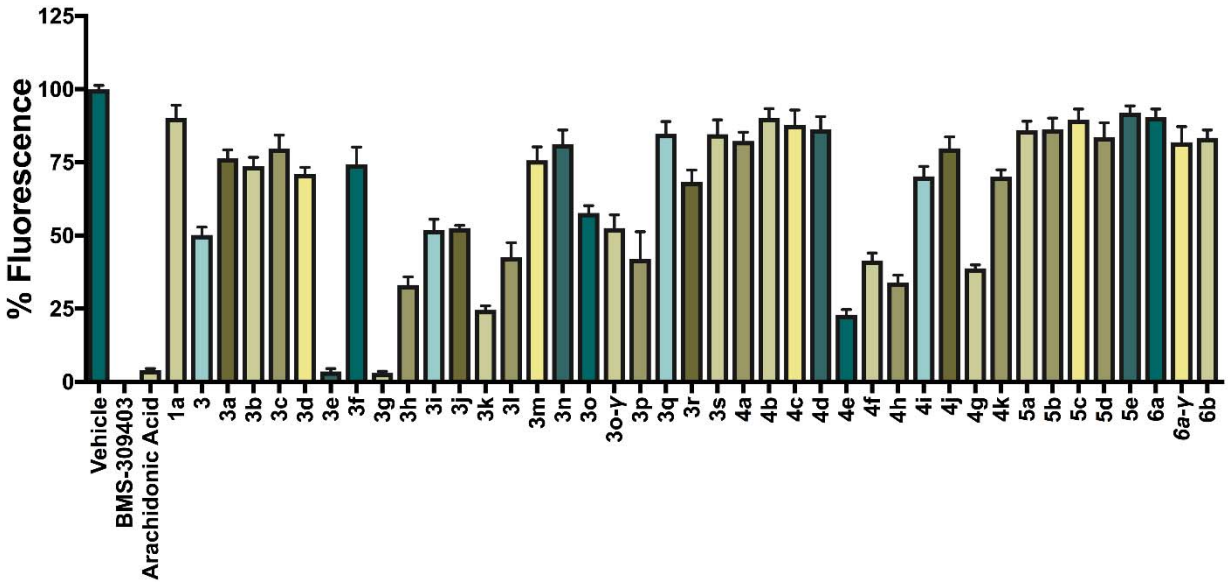
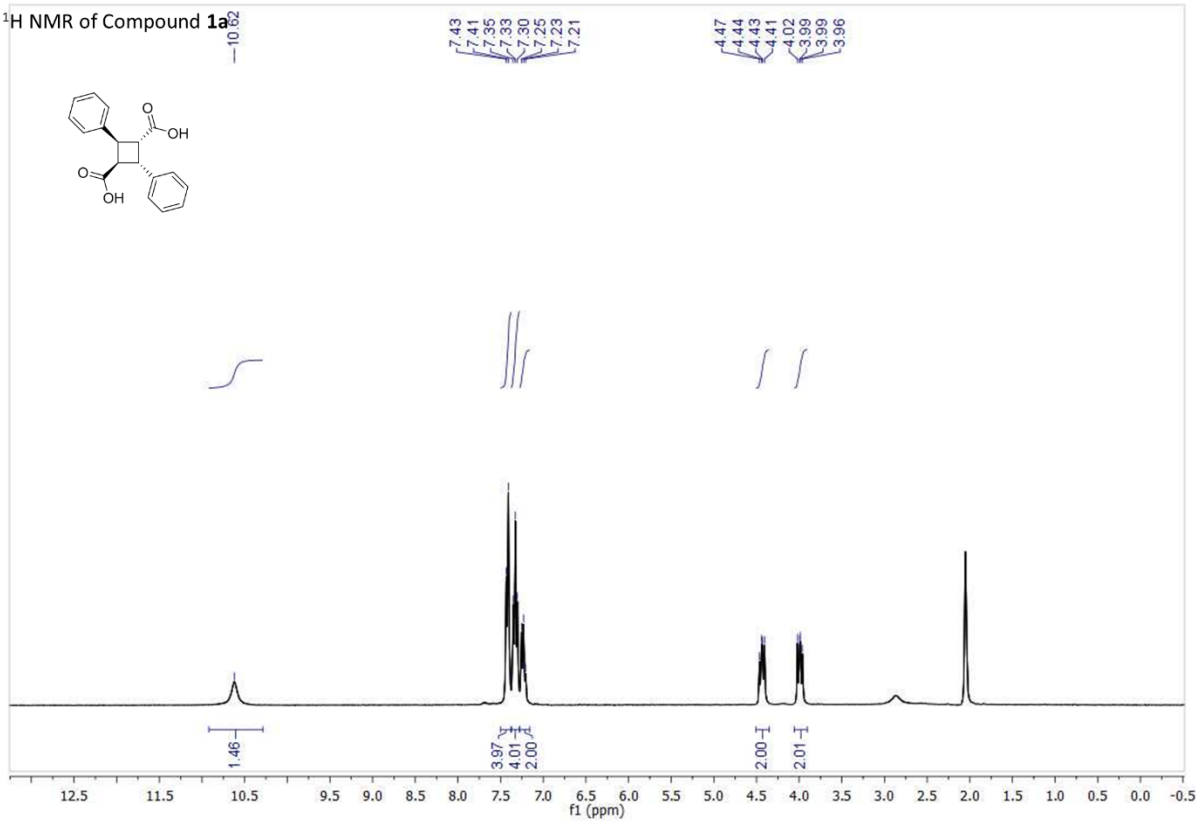
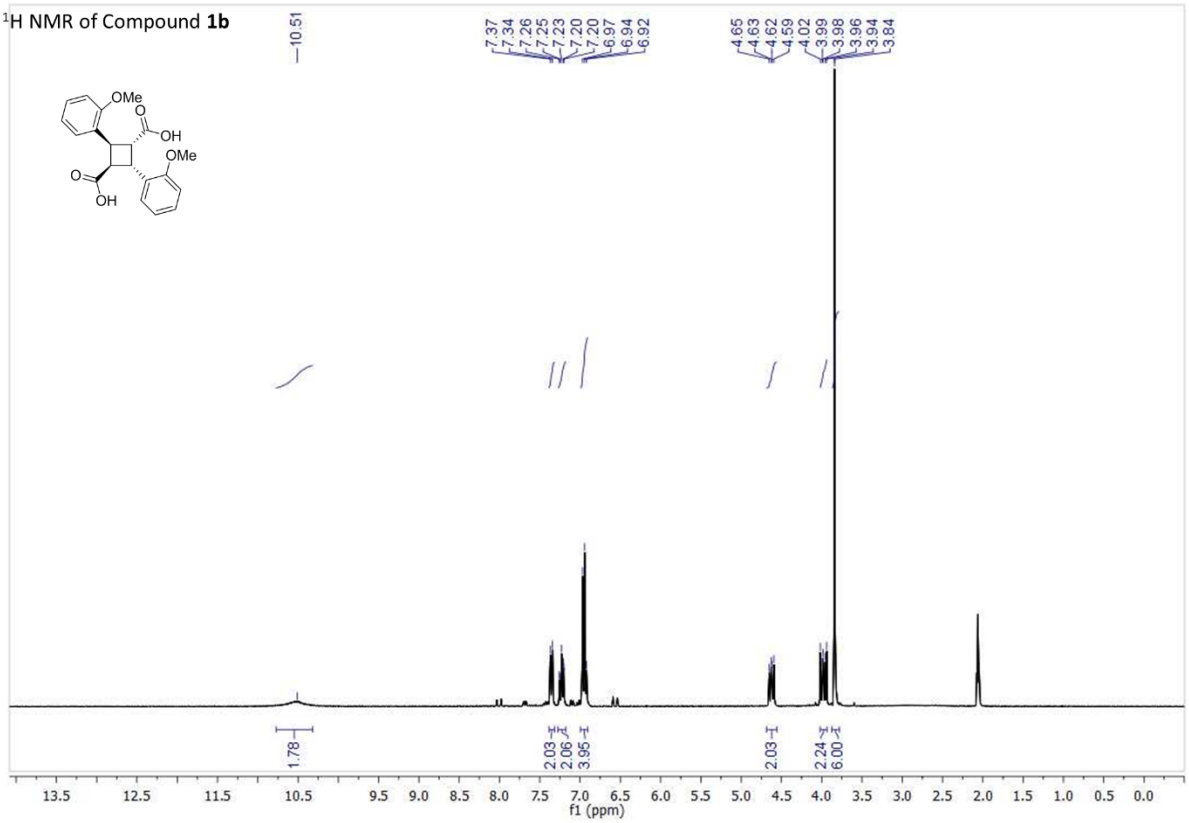


Figure S5. Binding of inhibitors to FABP4. Displacement of ANS from purified human FABP4 by each compound (10 μM). Data expressed as mean ± SEM relative to vehicle.

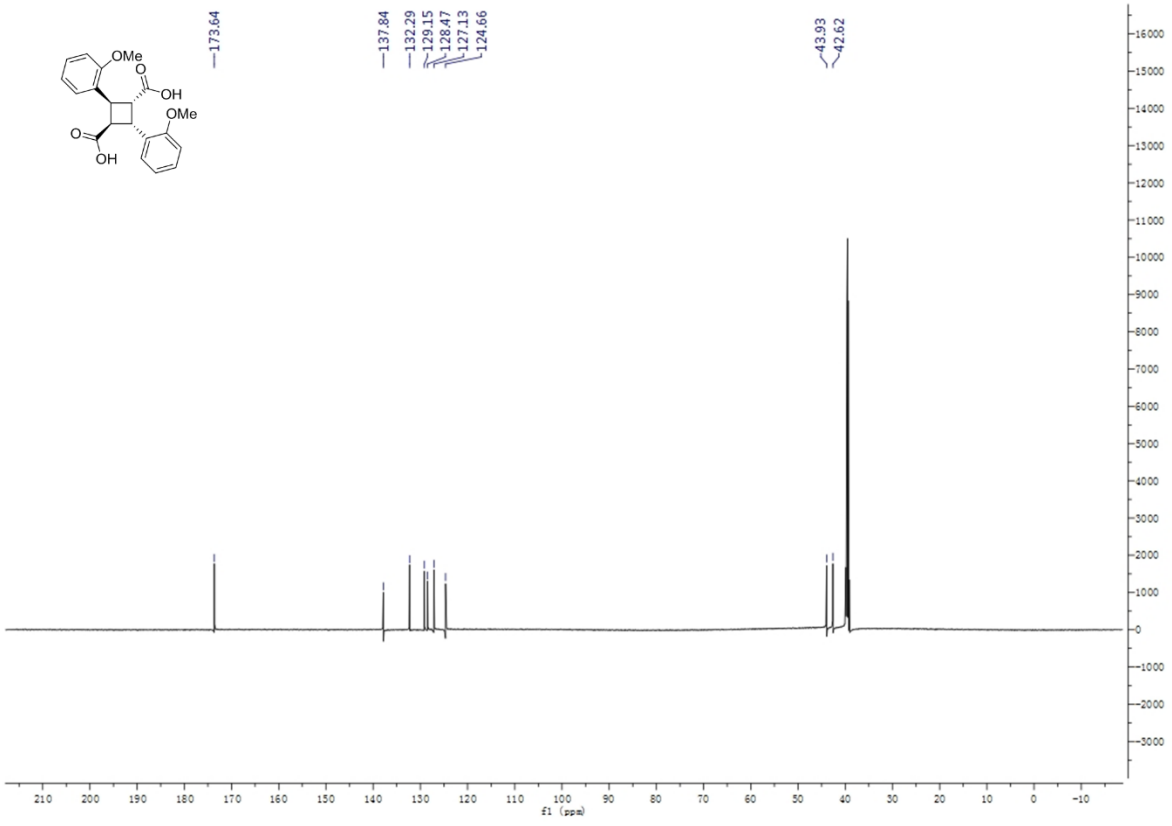
^{1}H NMR of Compound **1a**



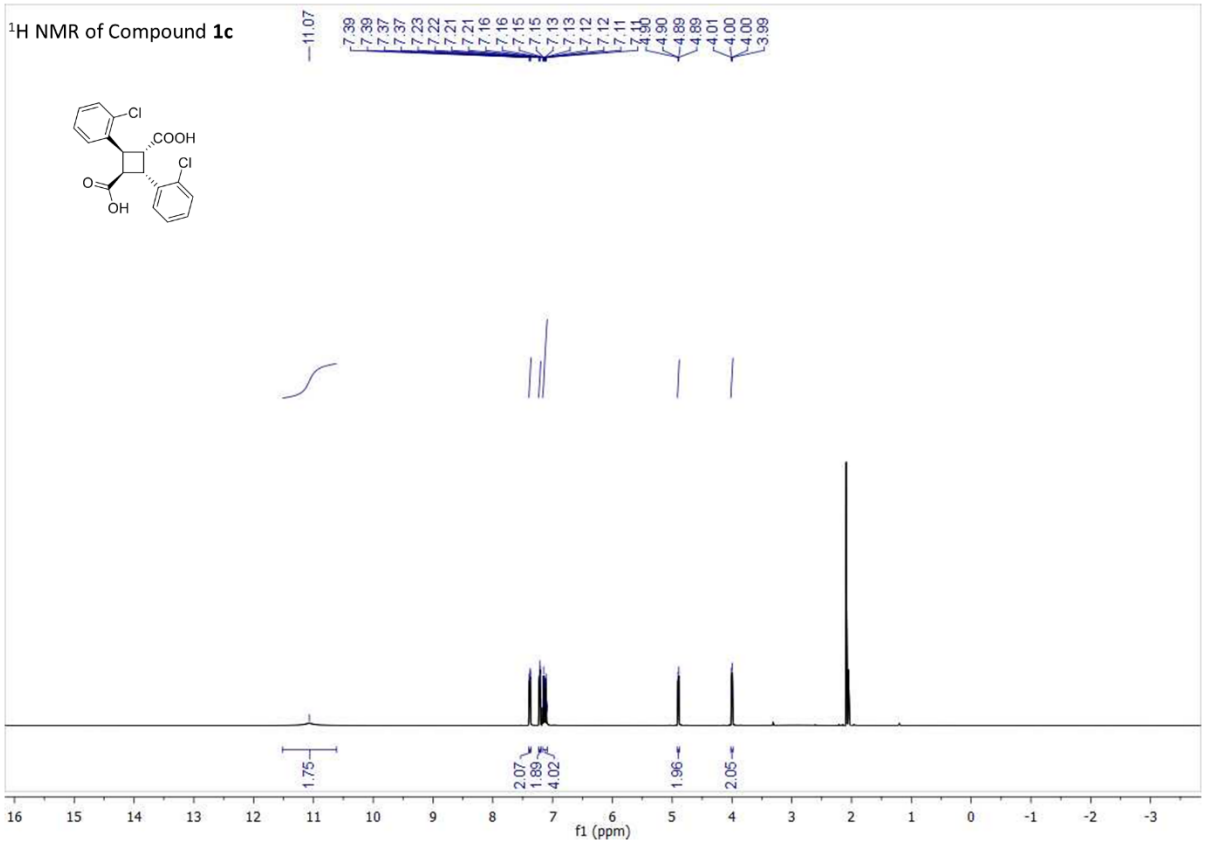
^{1}H NMR of Compound **1b**



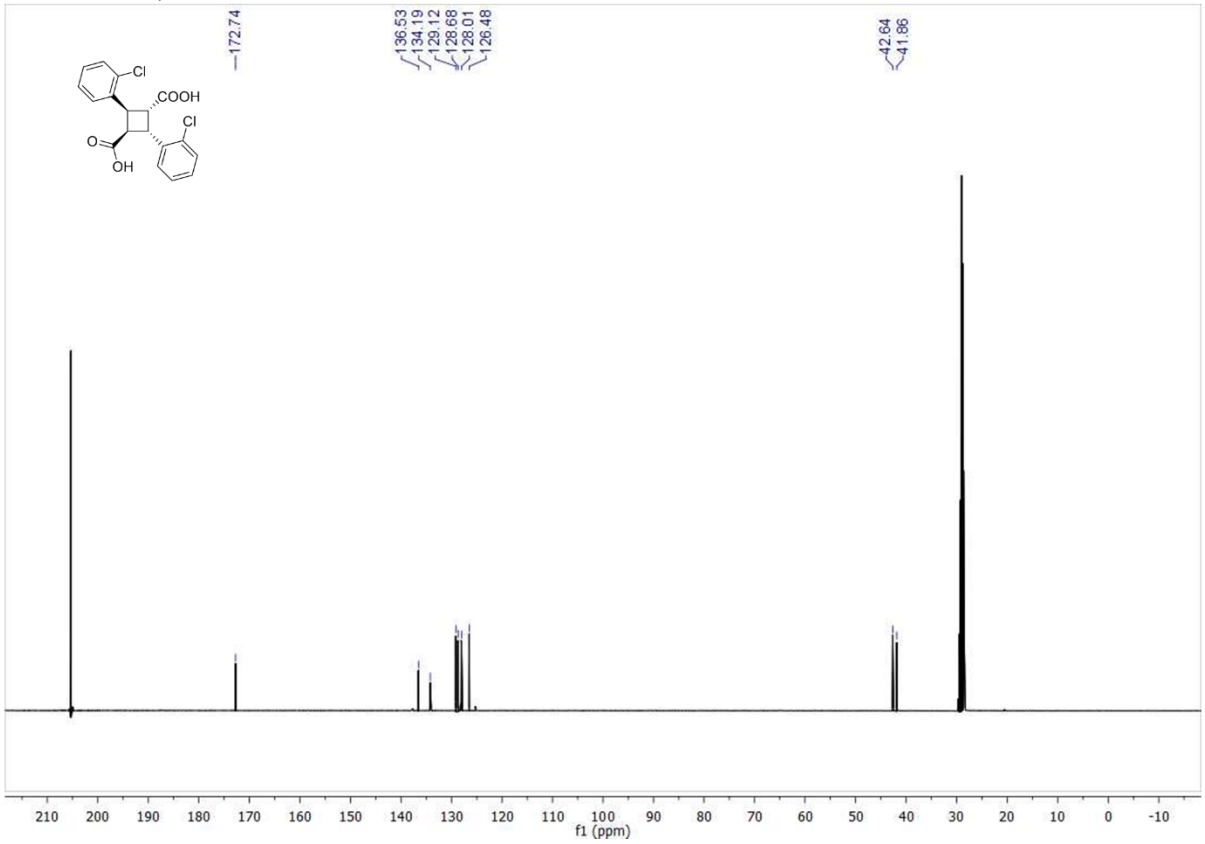
^{13}C NMR of Compound **1b**



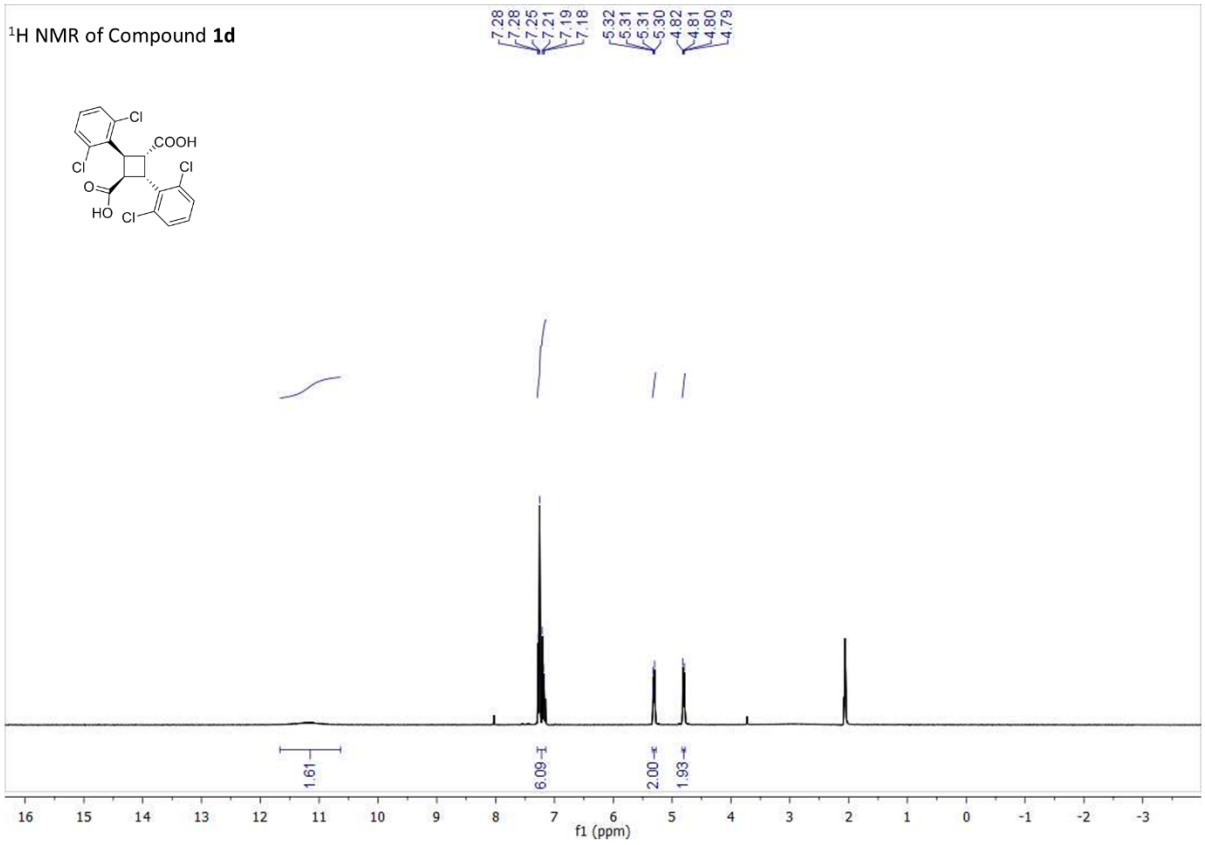
^{1}H NMR of Compound **1c**



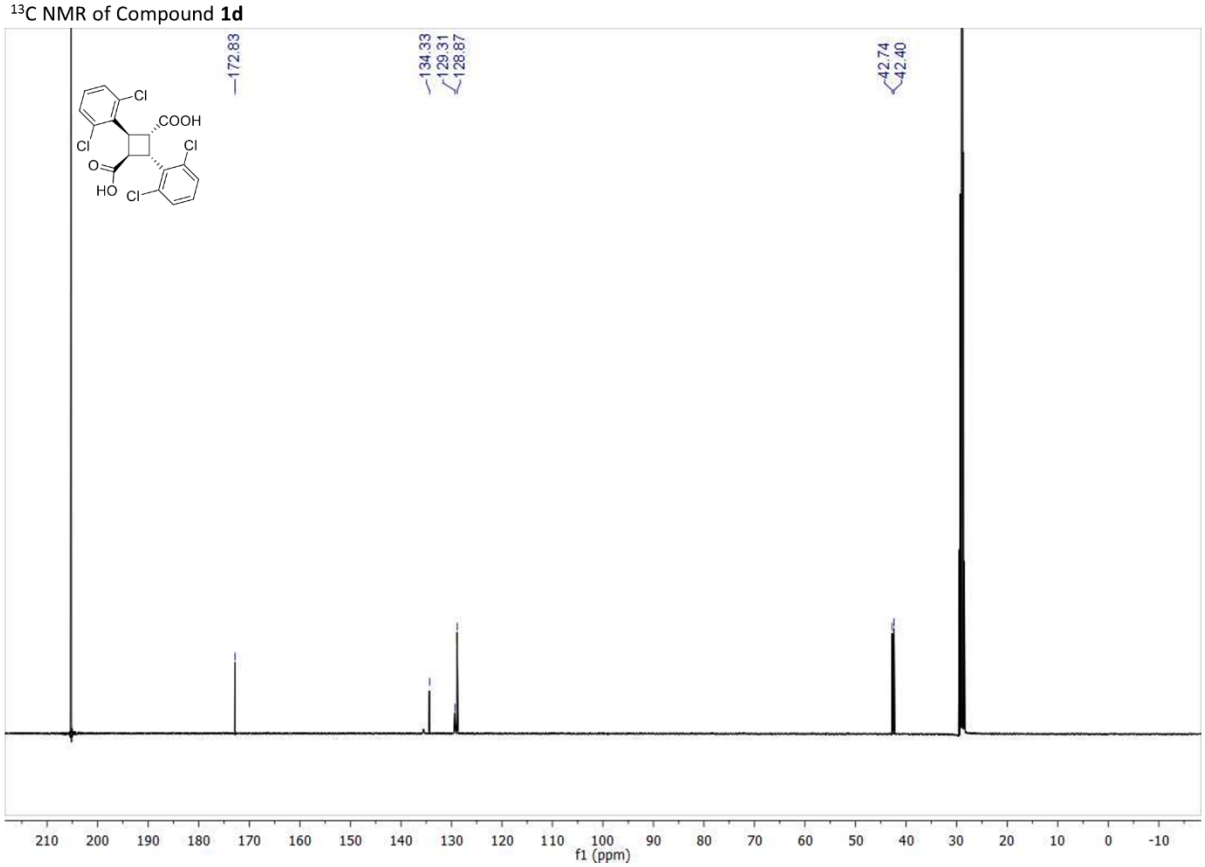
^{13}C NMR of Compound **1c**



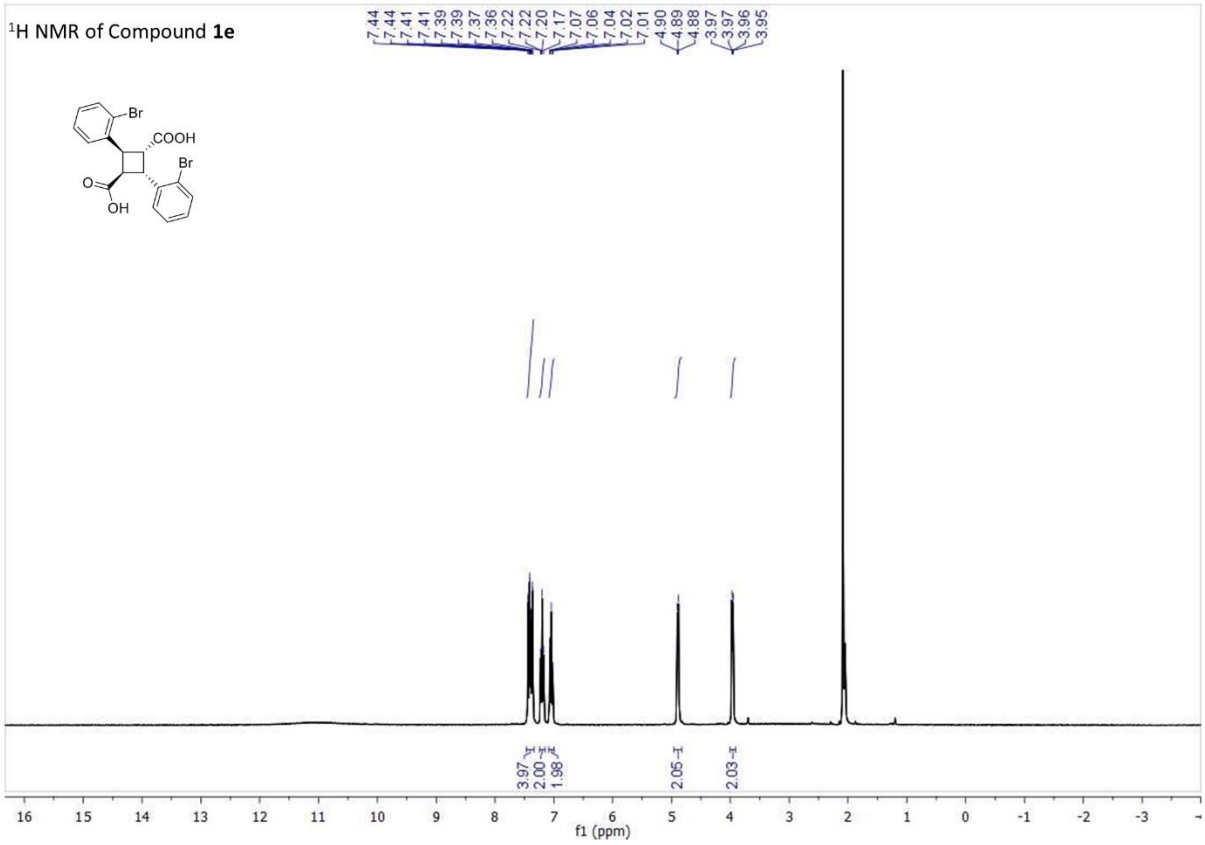
^{1}H NMR of Compound **1d**



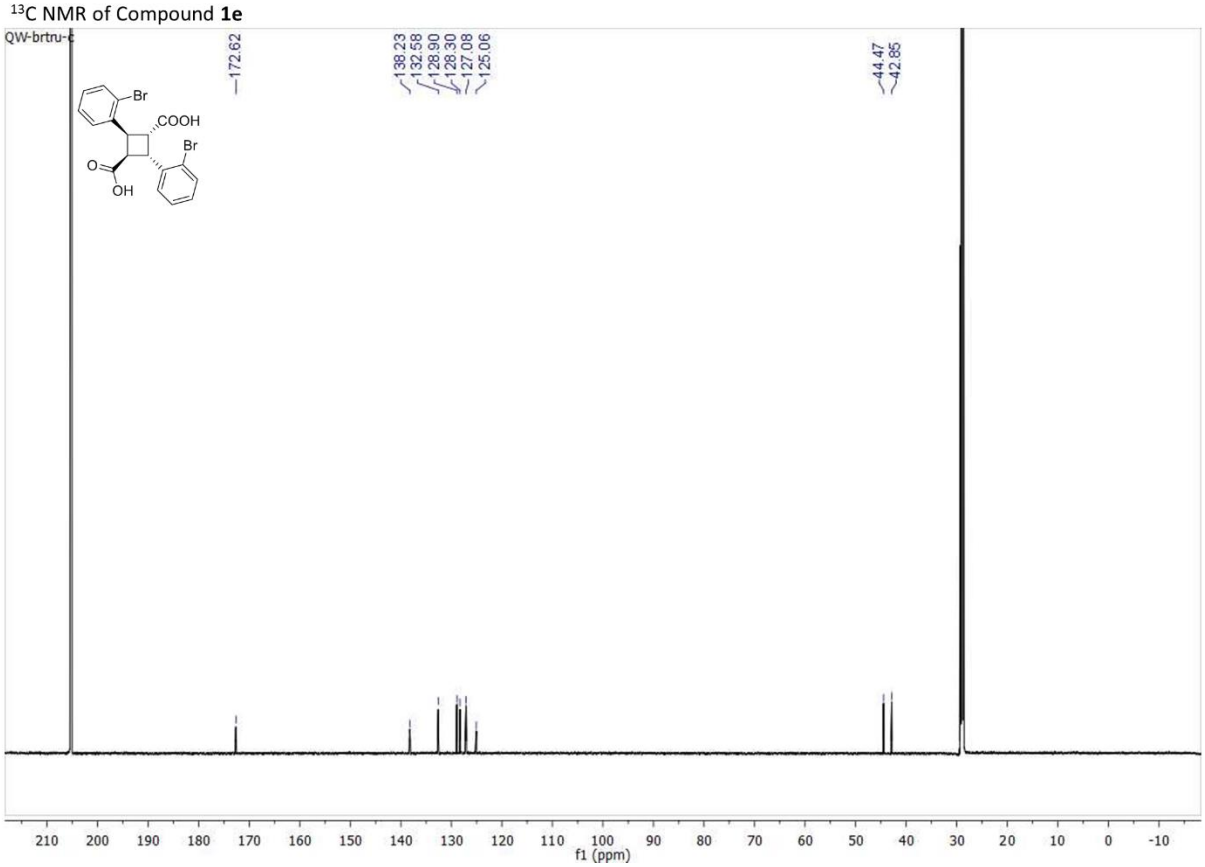
^{13}C NMR of Compound **1d**



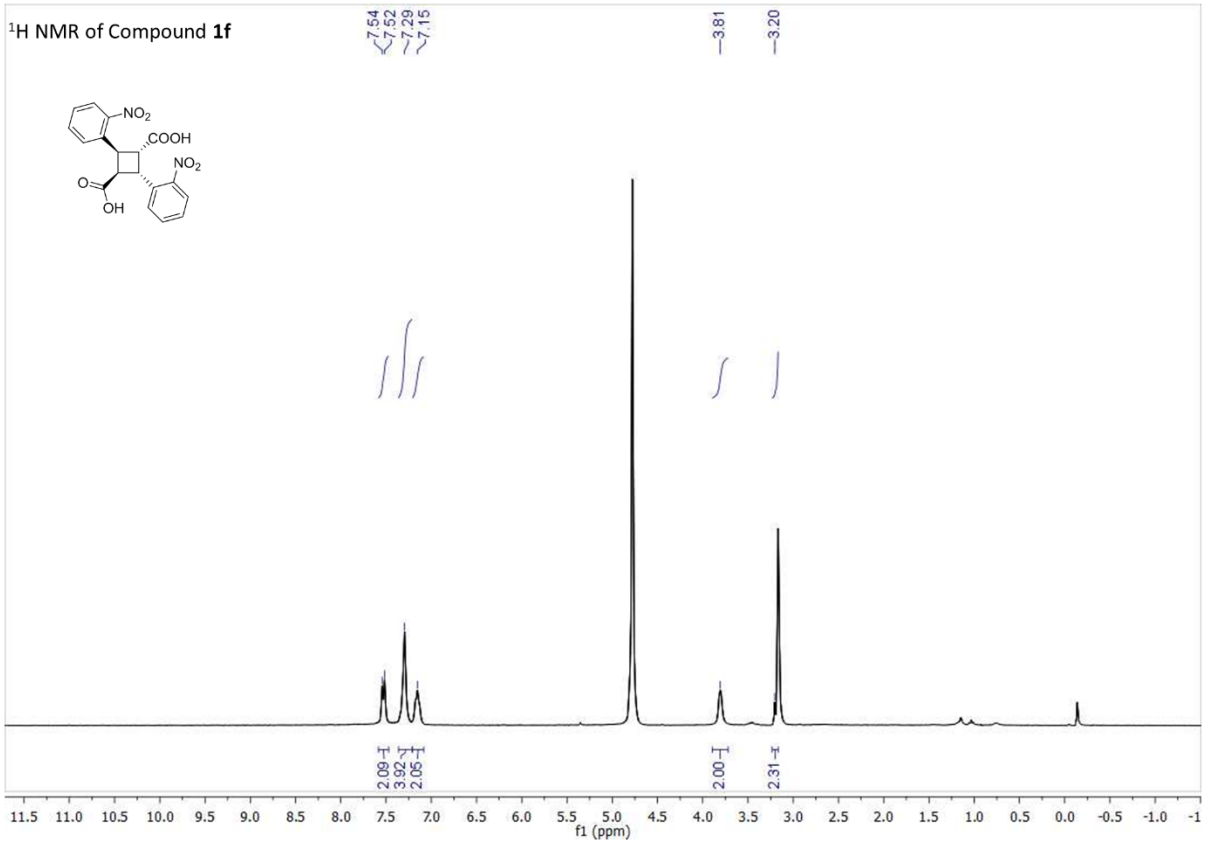
^{1}H NMR of Compound **1e**



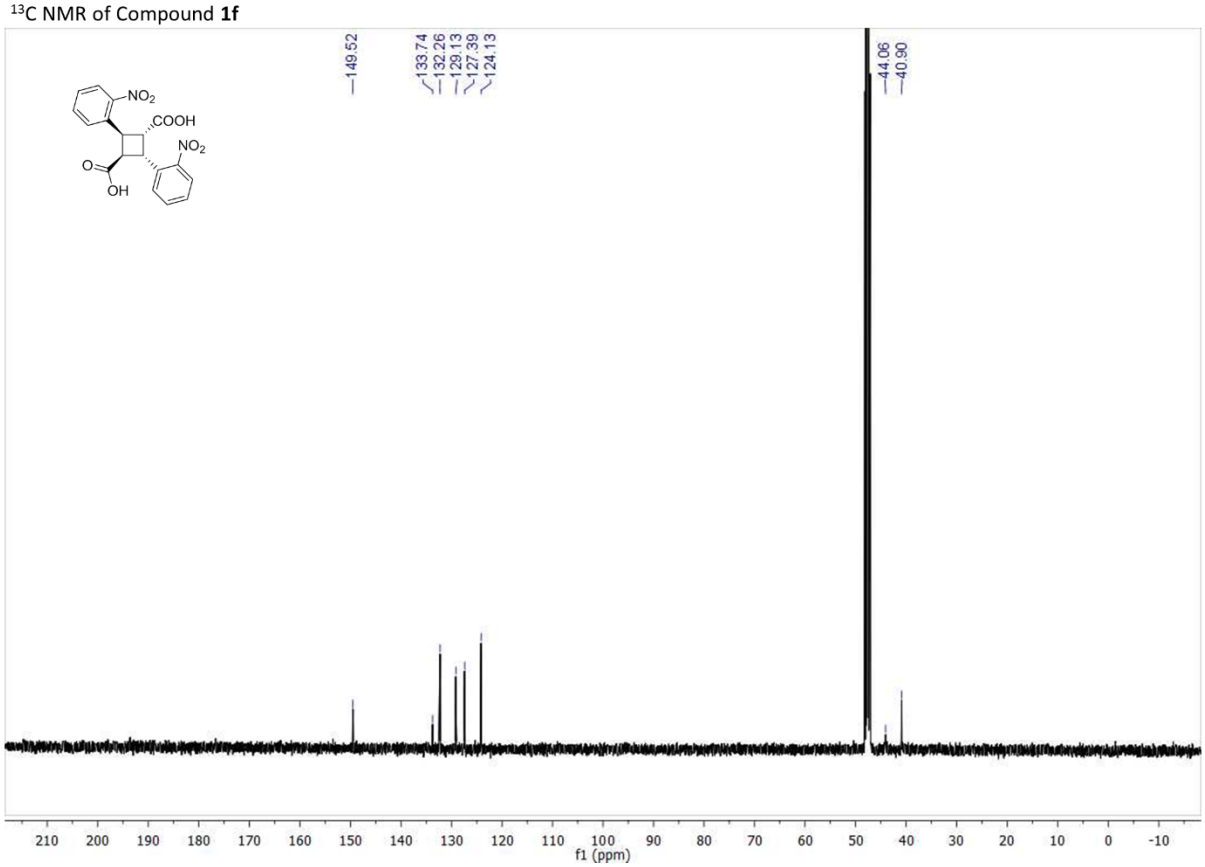
^{13}C NMR of Compound **1e**



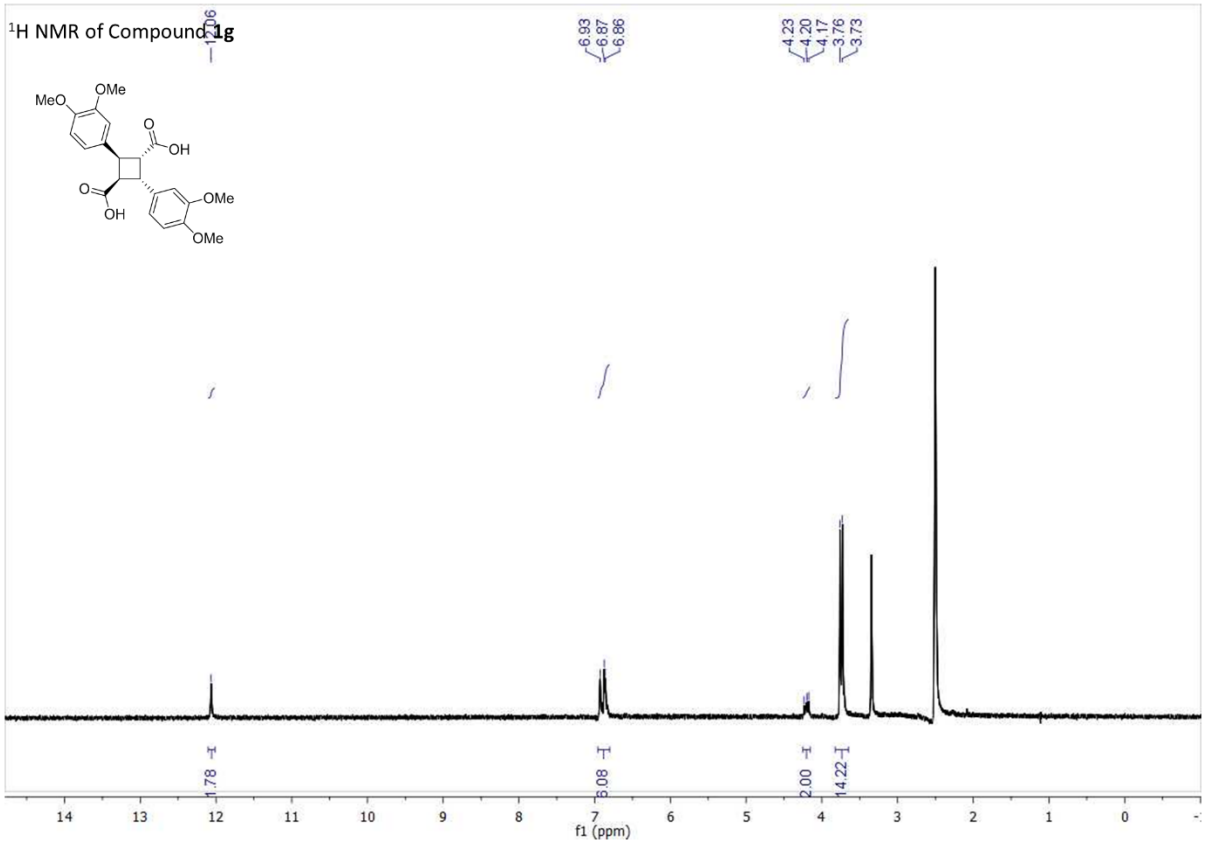
^{1}H NMR of Compound **1f**



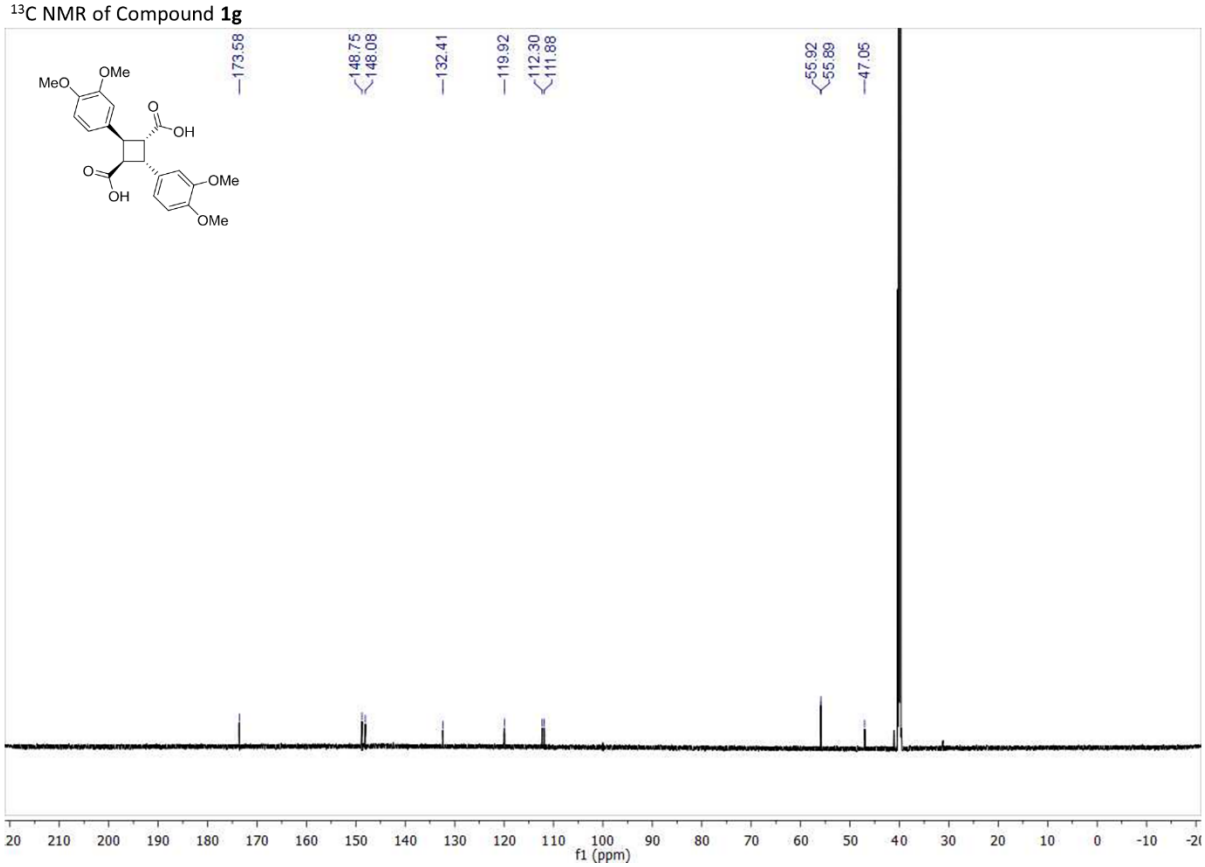
^{13}C NMR of Compound **1f**

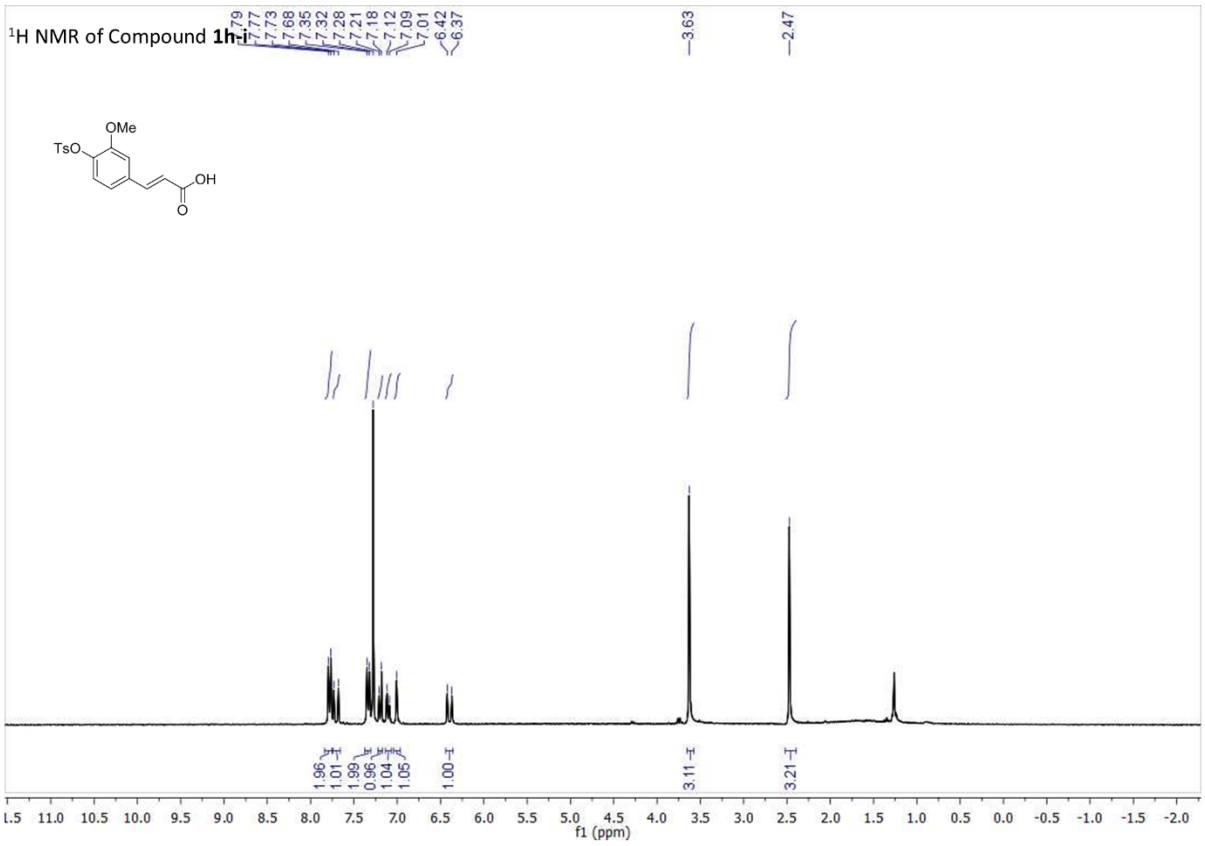


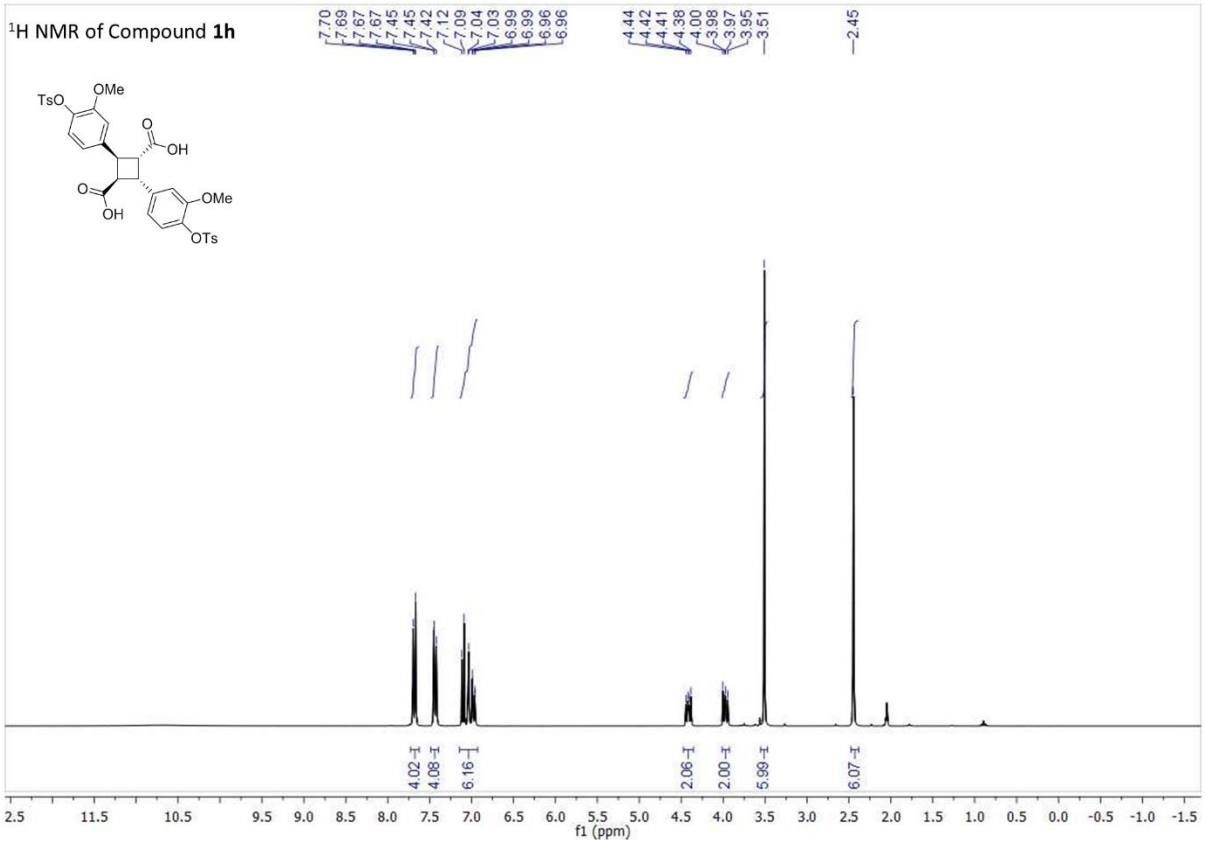
^{1}H NMR of Compound **1g**

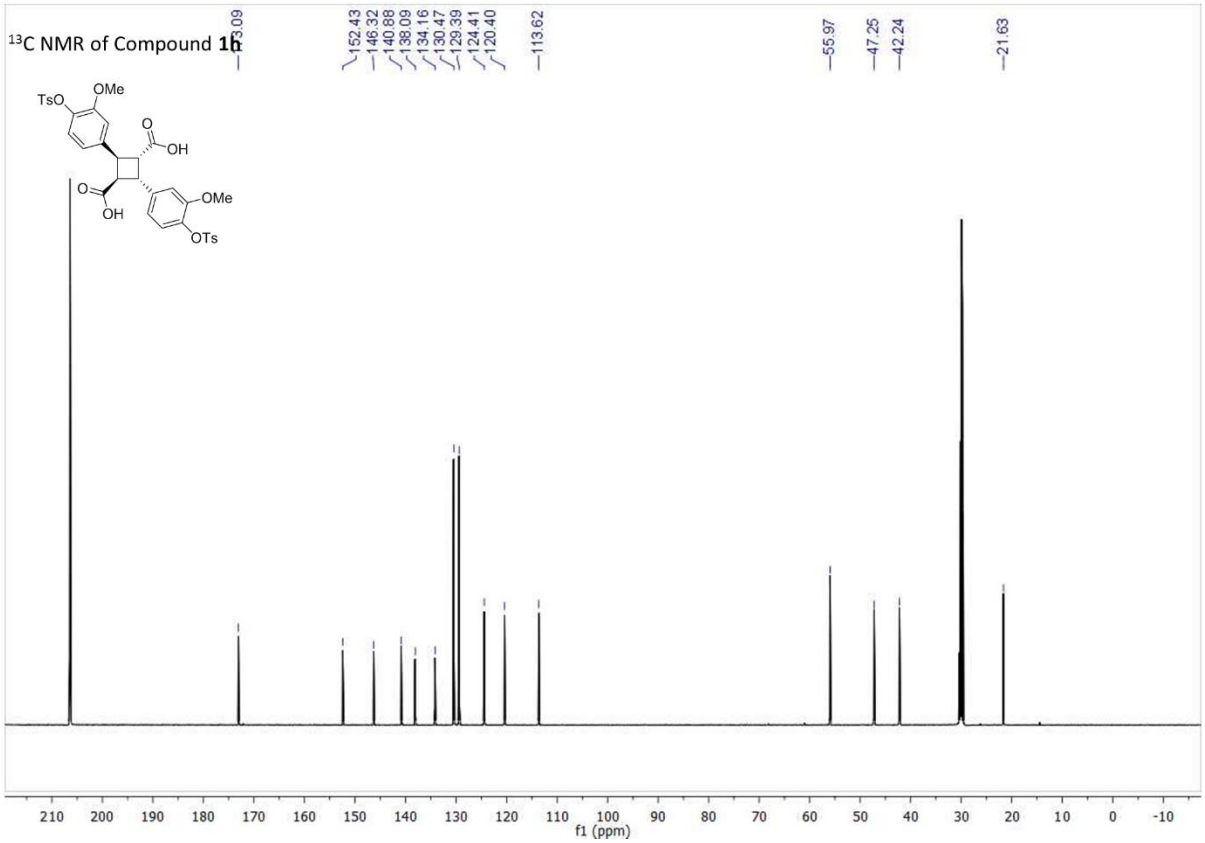


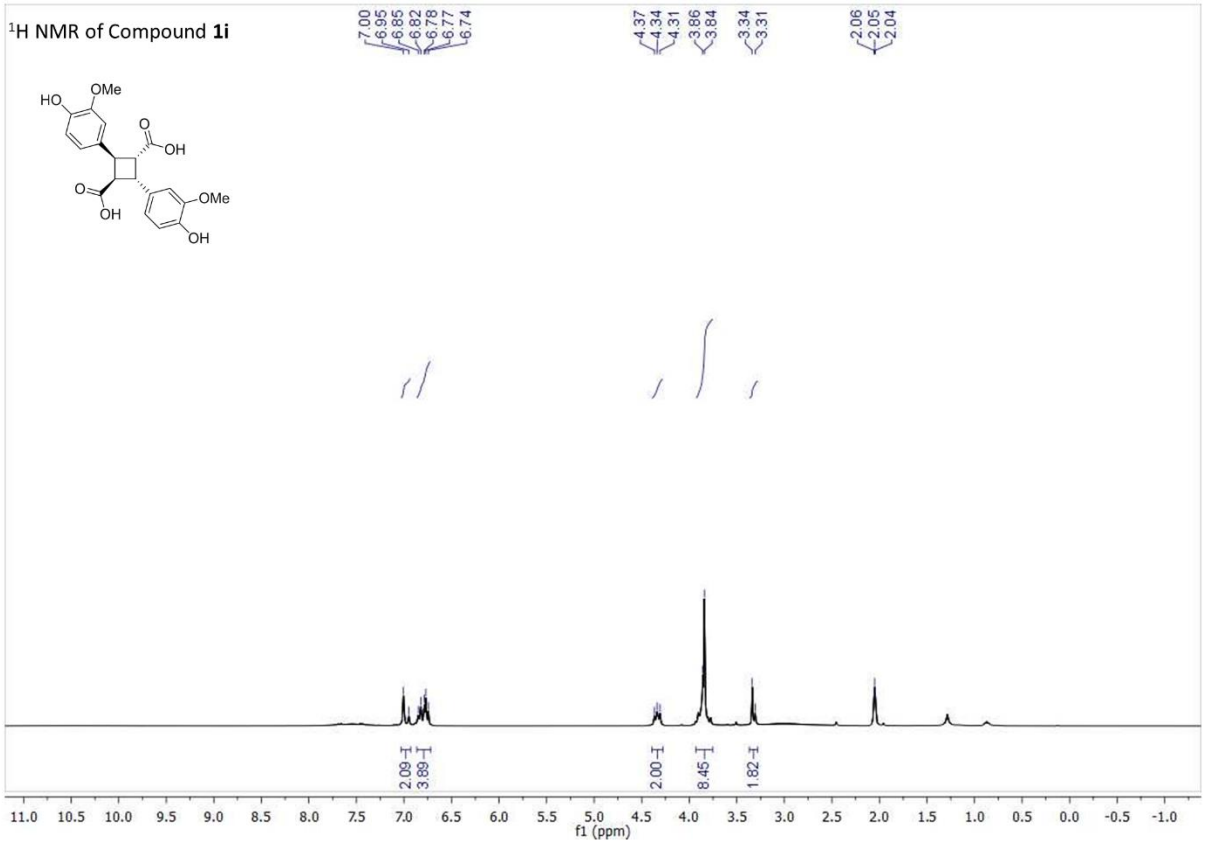
^{13}C NMR of Compound **1g**

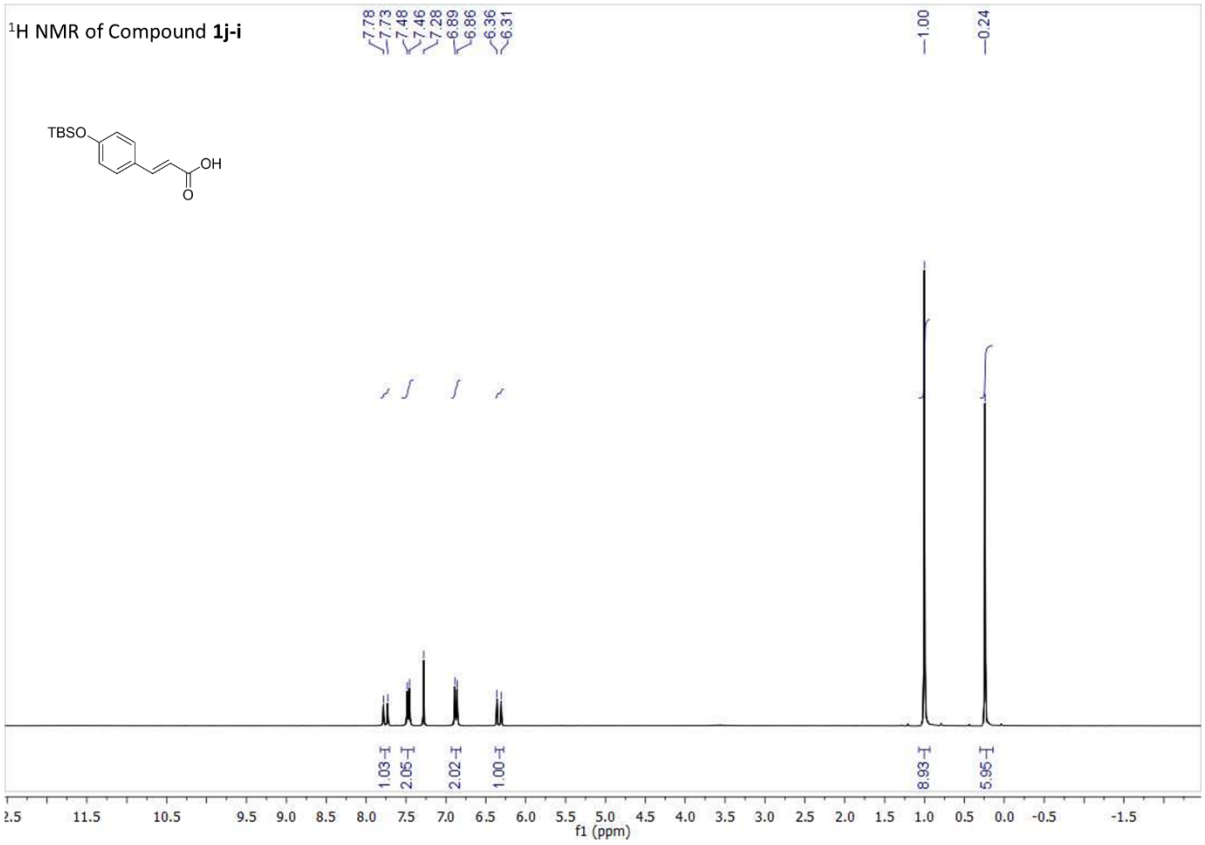



^{1}H NMR of Compound **1h-i**
7.79
7.77
7.73
7.68
7.35
7.32
7.28
7.21
7.18
7.12
7.09
7.01
6.42
6.37
3.63
2.47
OMe
TsO
OH
O
1.96
1.01
1.99
0.96
1.04
1.05
1.00
3.11
3.21
f1 (ppm)

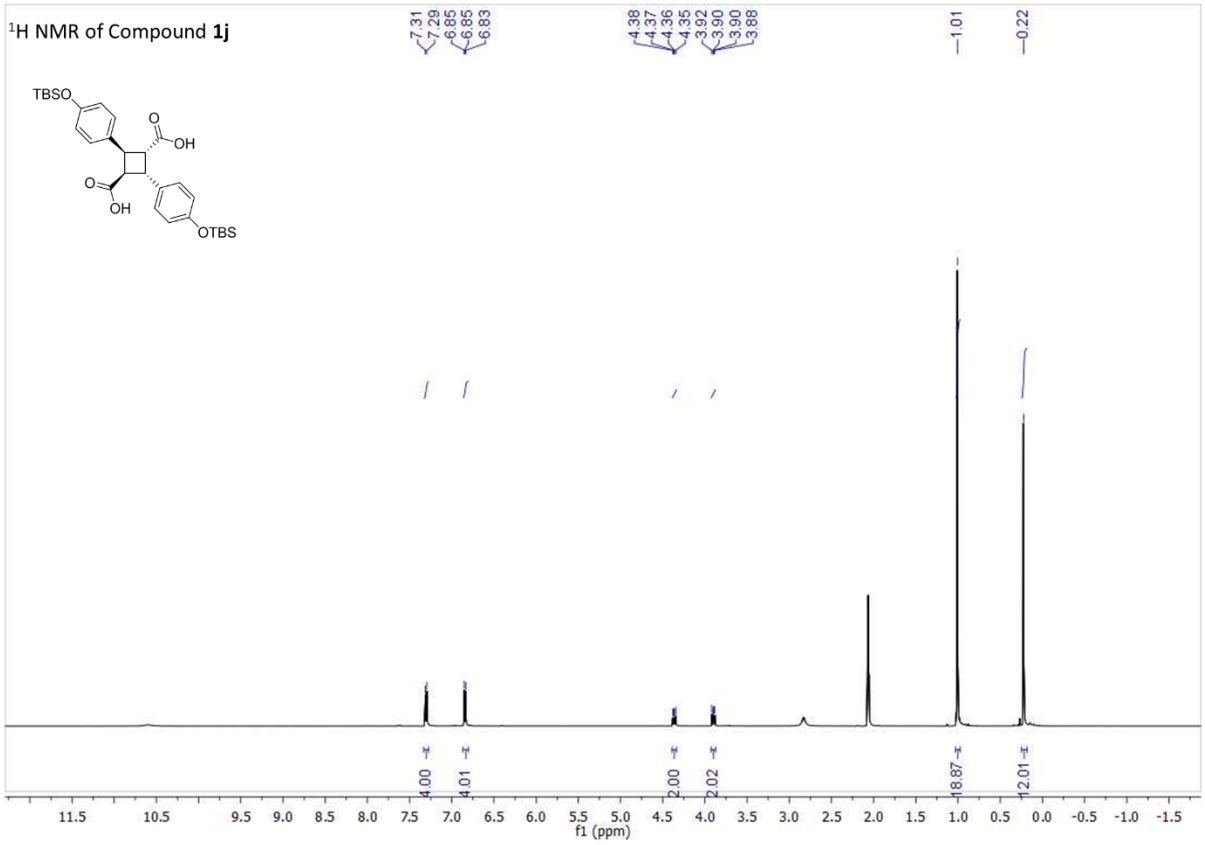

1H NMR of Compound 1h
7.70
7.69
7.67
7.67
7.45
7.45
7.42
7.12
7.09
7.04
7.03
6.99
6.99
6.96
6.96
4.44
4.42
4.41
4.38
4.00
3.98
3.97
3.95
3.51
2.45
TsO
OMe
O
OH
O
OH
OMe
OTs
4.02
4.08
6.16
2.06
2.00
5.99
6.07
f1 (ppm)


13C NMR of Compound 1h
173.09
152.43
146.32
140.88
138.09
134.16
130.47
129.39
124.41
120.40
113.62
55.97
47.25
42.24
21.63
TsO
OMe
O
OH
O
OH
OMe
OTs
f1 (ppm)

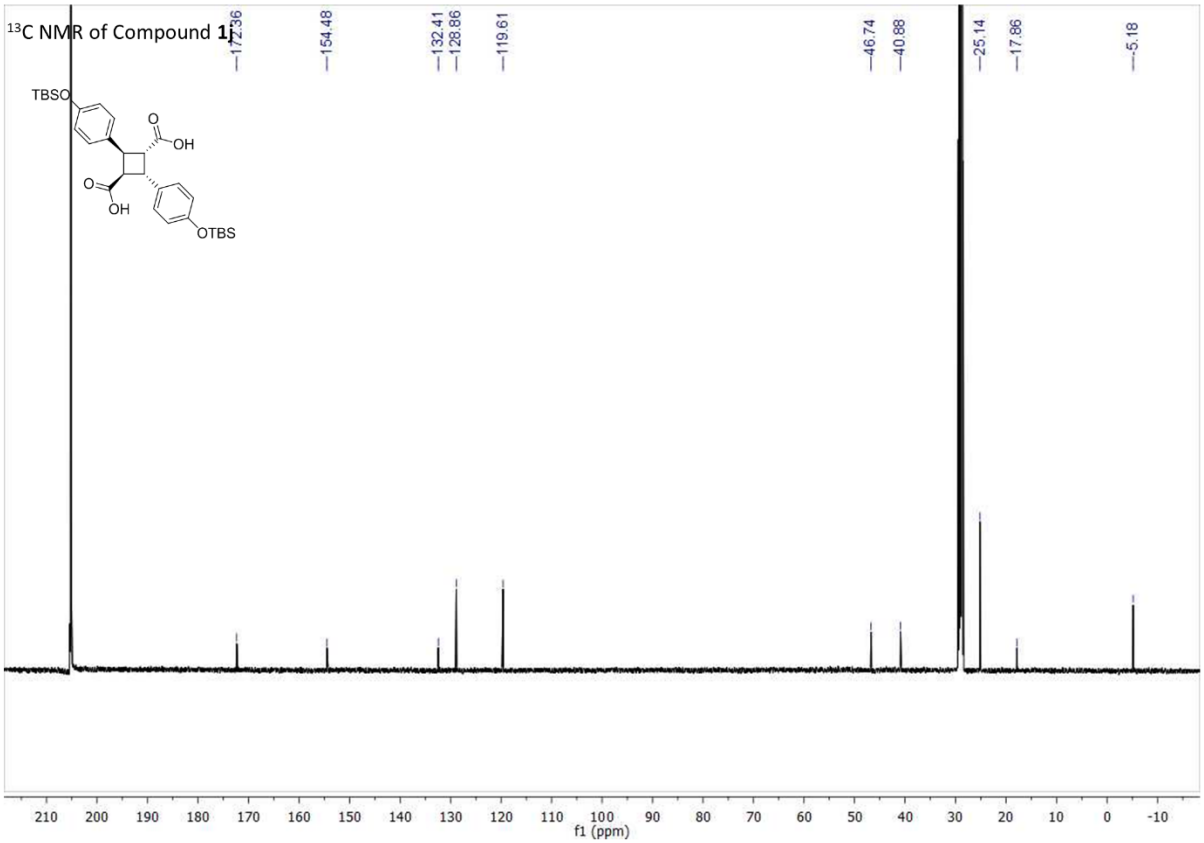

¹H NMR of Compound 1i
HO
OMe
O
OH
O
OH
OMe
OH
7.00
6.95
6.85
6.82
6.78
6.77
6.74
4.37
4.34
4.31
3.86
3.84
3.34
3.31
2.06
2.05
2.04
2.09
3.89
2.00
8.45
1.82
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)


^{1}H NMR of Compound **1j-i**
TBSO
OH
O
7.78
7.73
7.48
7.46
7.28
6.89
6.86
6.36
6.31
1.00
0.24
1.03
2.05
2.02
1.00
8.93
5.95
f1 (ppm)

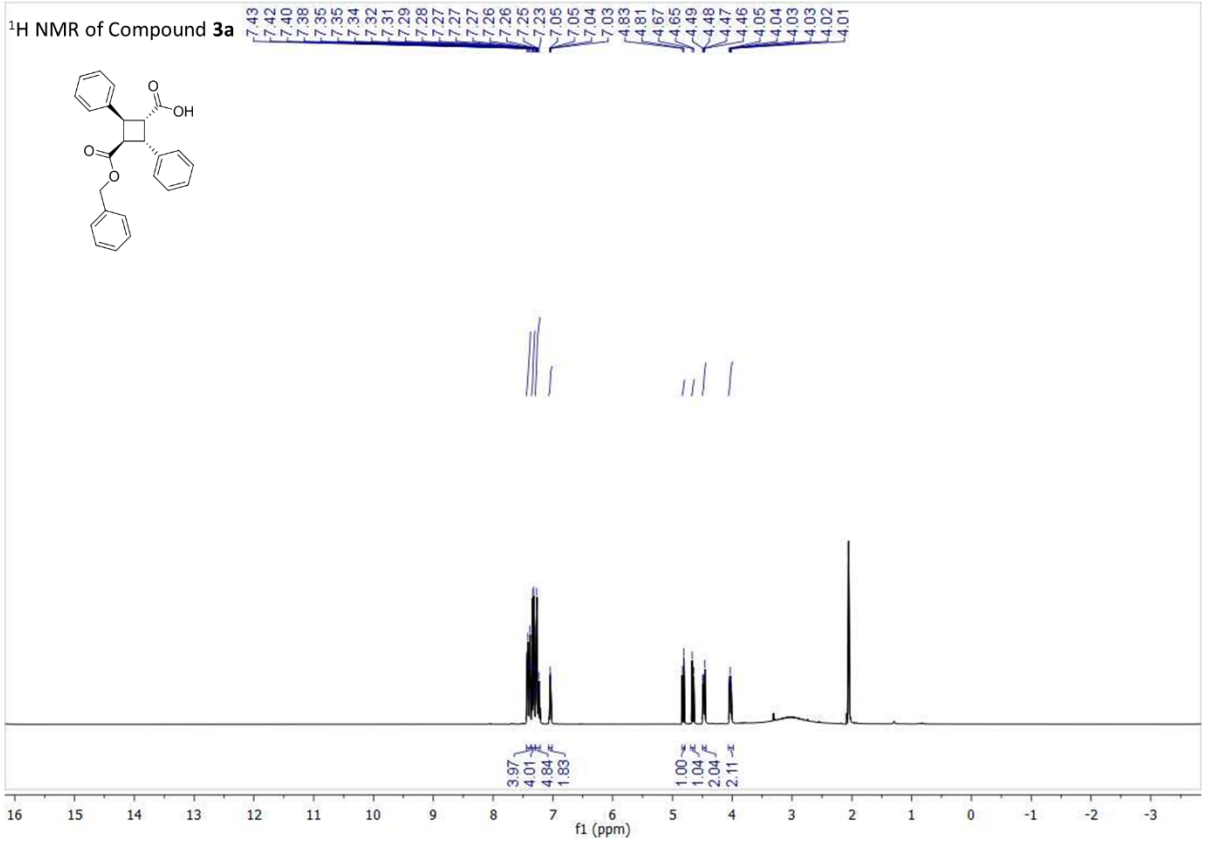
^{1}H NMR of Compound **1j**



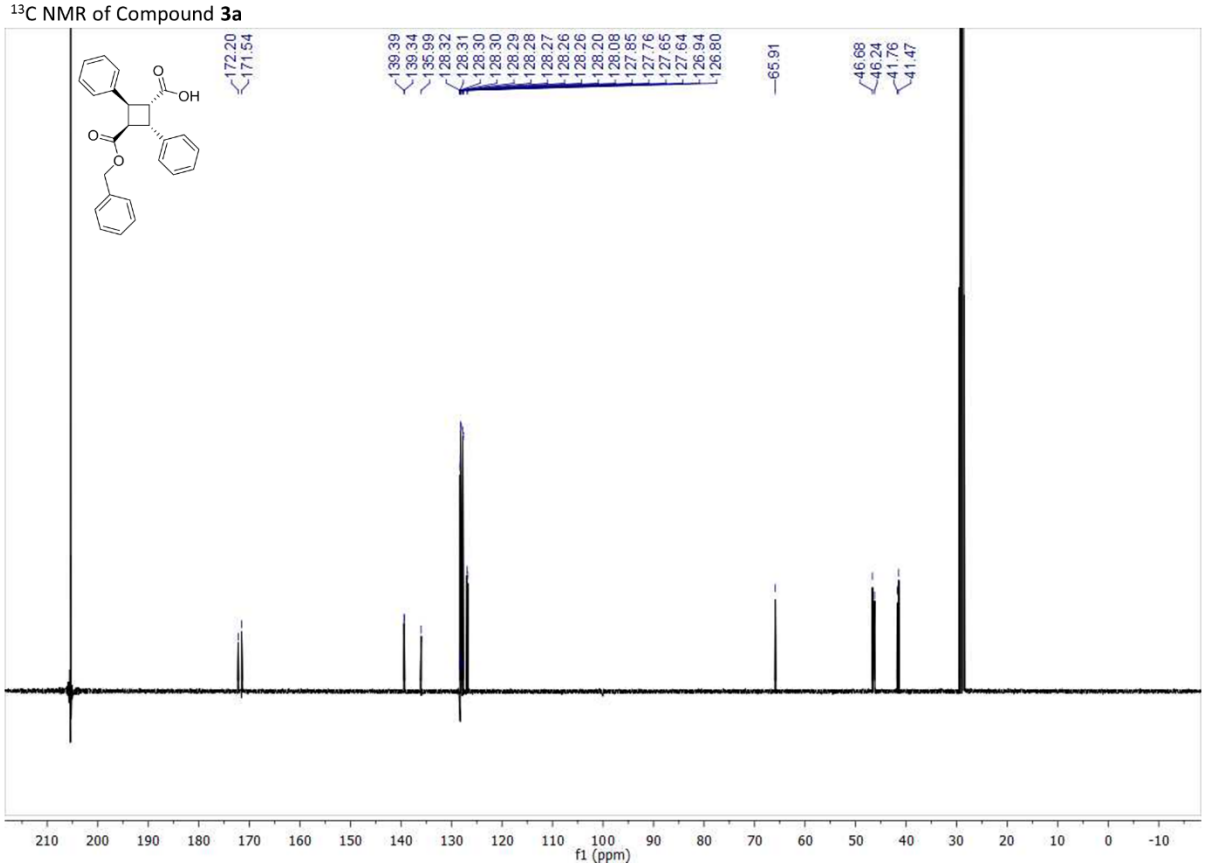
^{13}C NMR of Compound **1j**



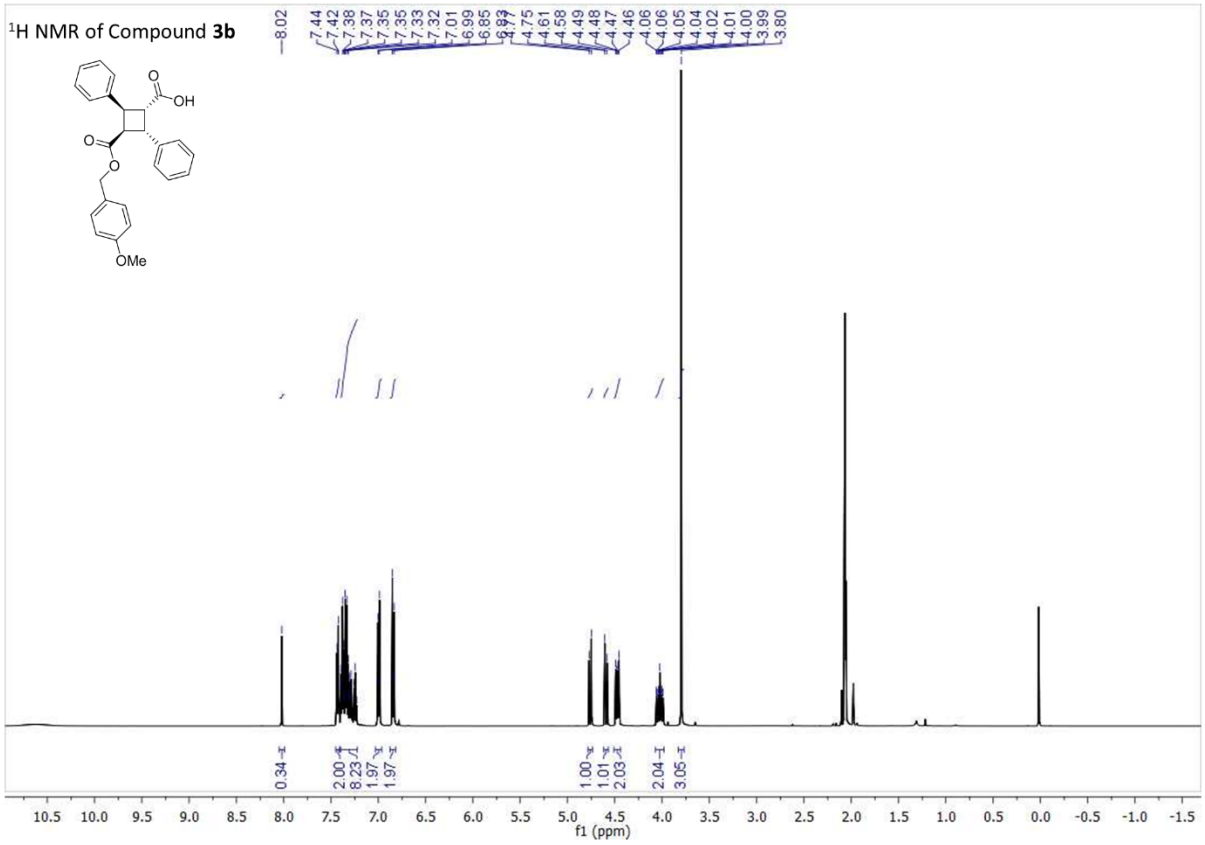
^{1}H NMR of Compound **3a**



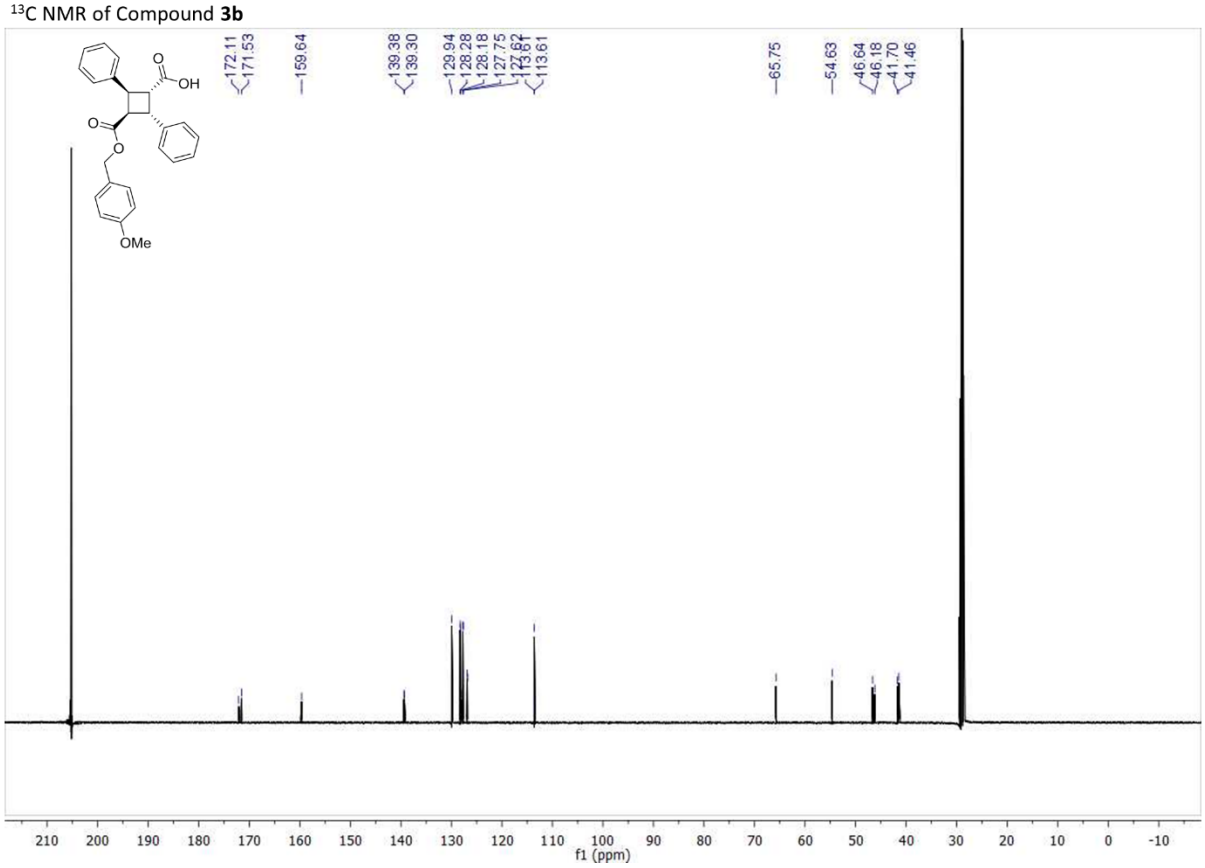
^{13}C NMR of Compound **3a**



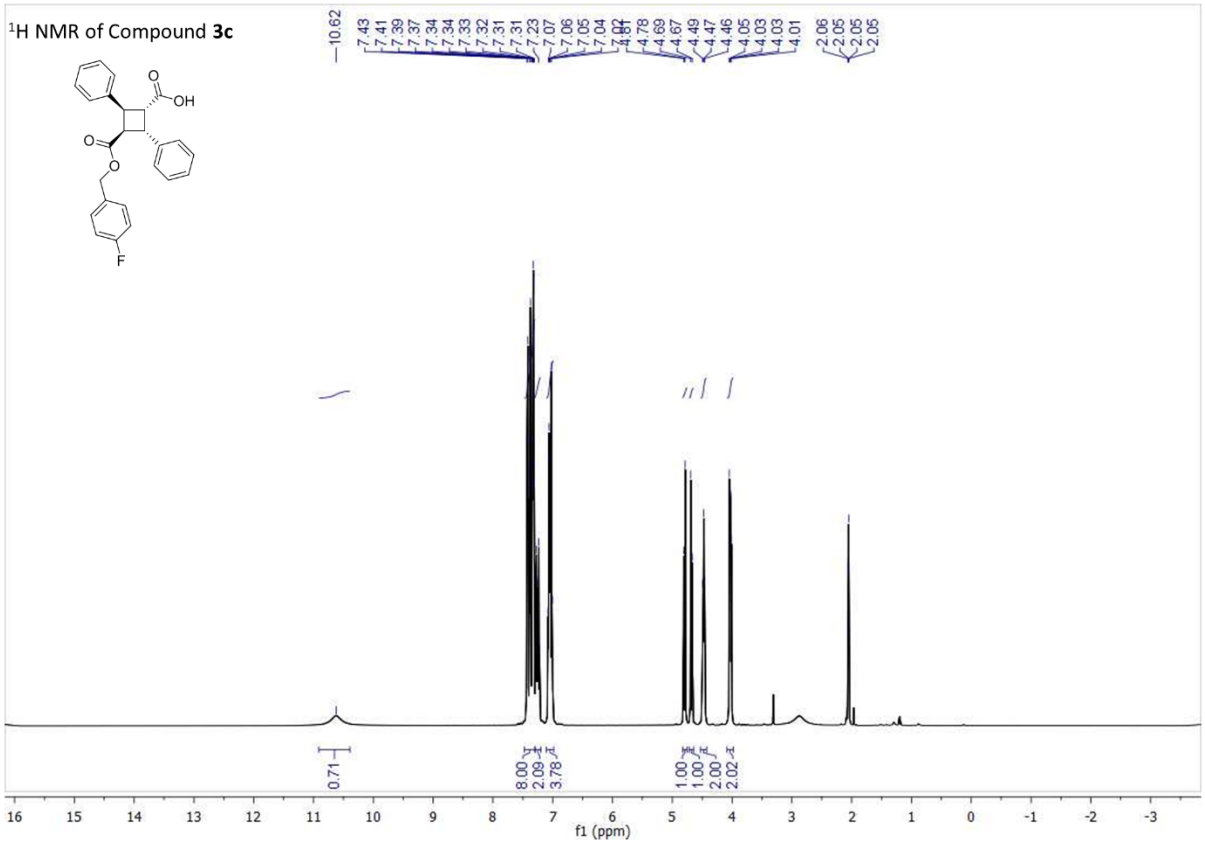
^{1}H NMR of Compound **3b**



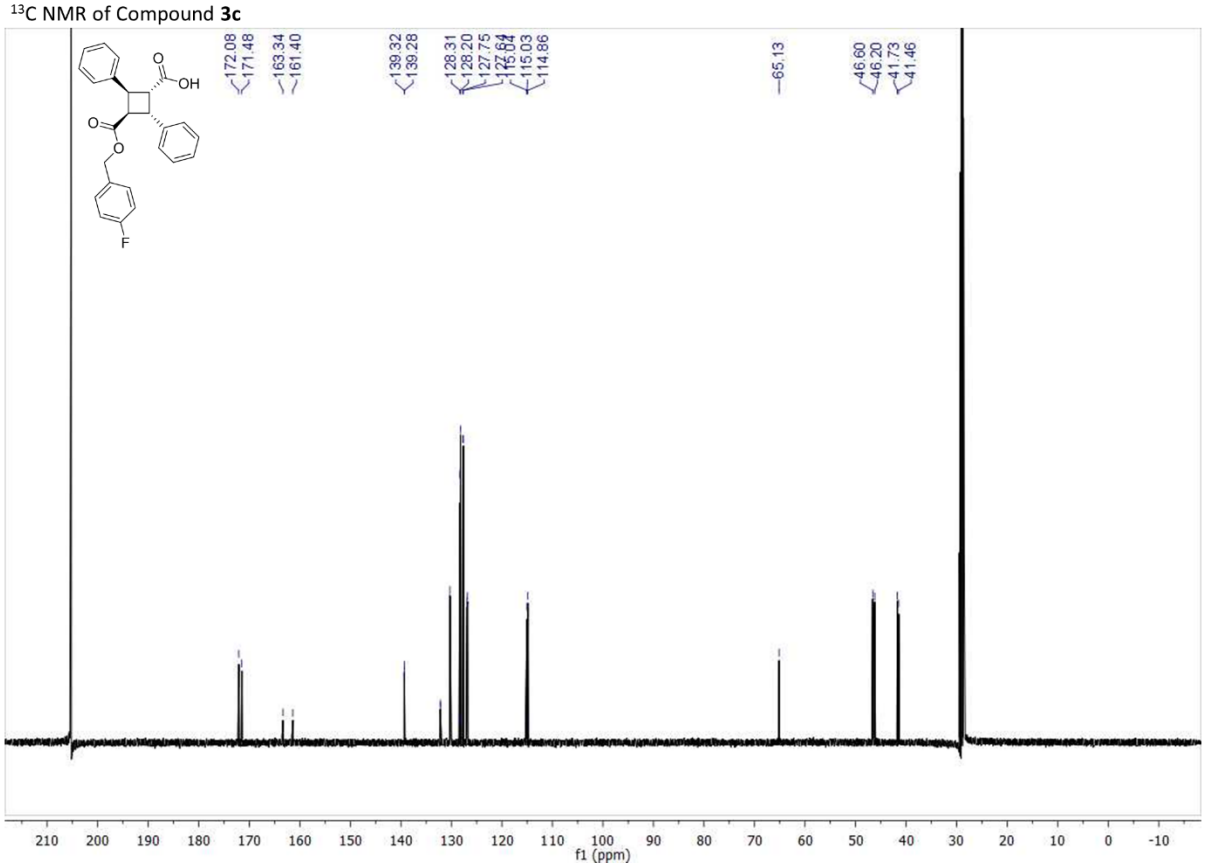
^{13}C NMR of Compound **3b**



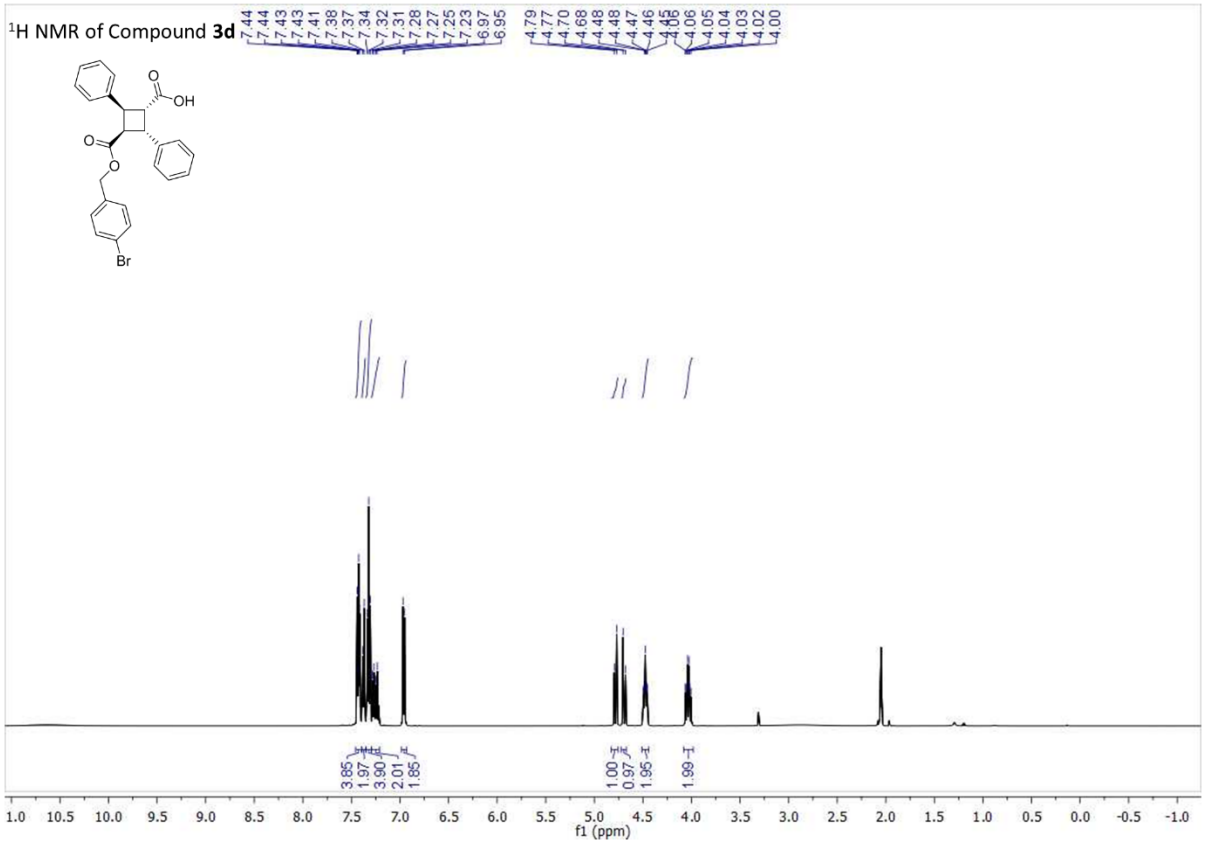
^{1}H NMR of Compound **3c**



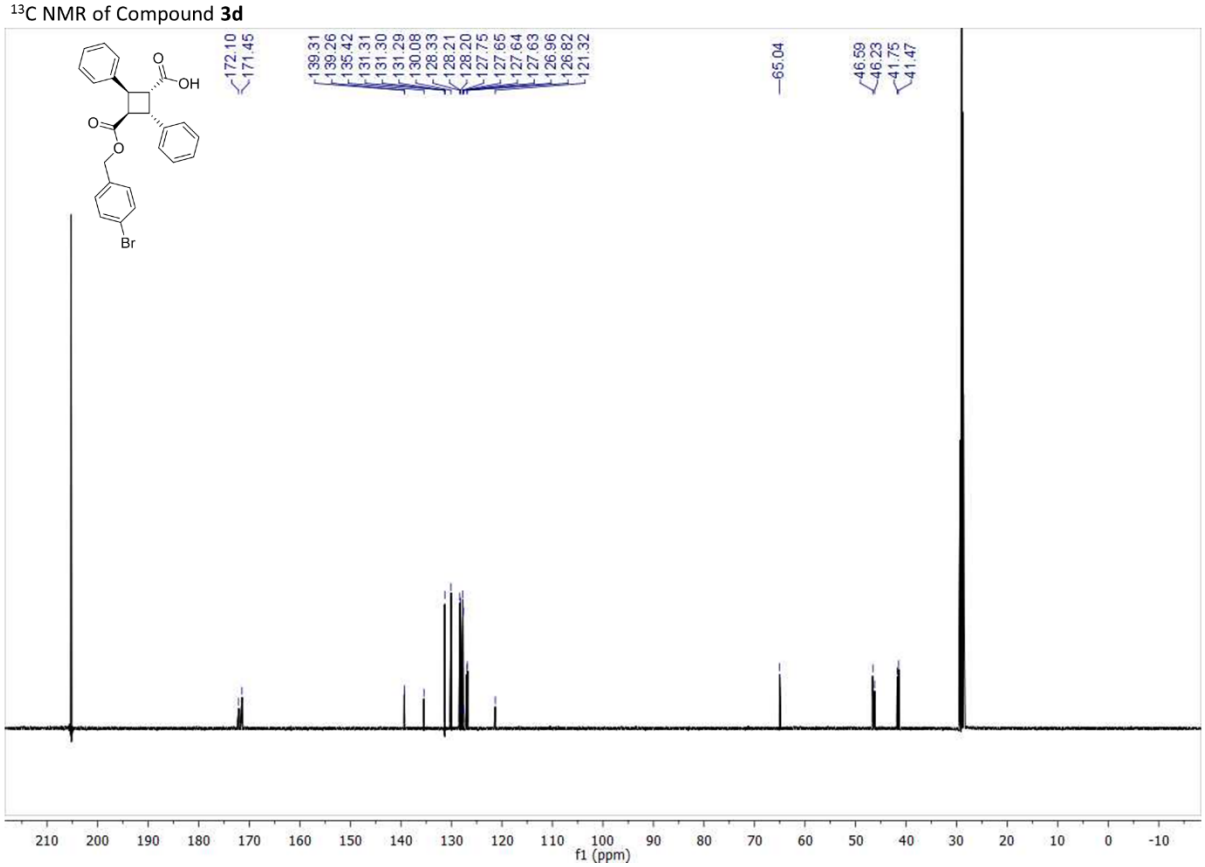
^{13}C NMR of Compound **3c**



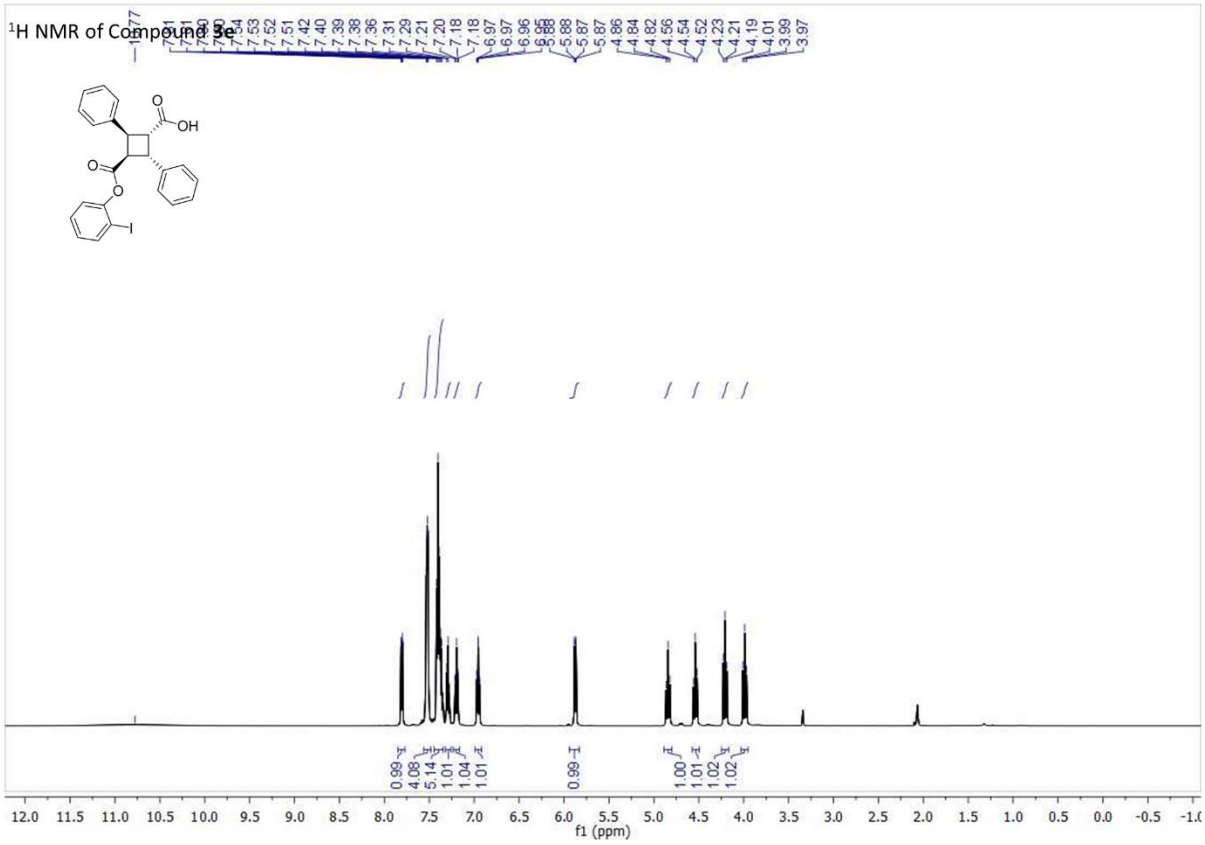
^{1}H NMR of Compound **3d**



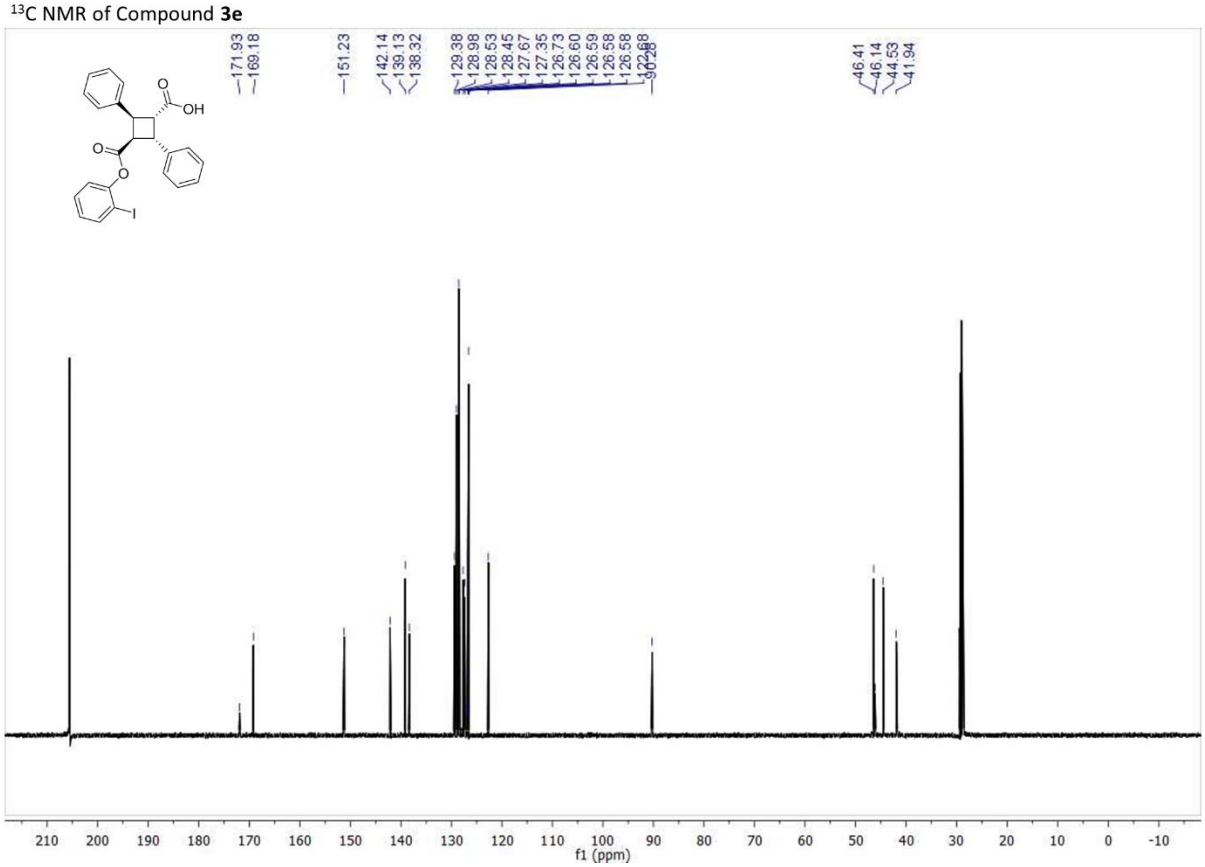
^{13}C NMR of Compound **3d**



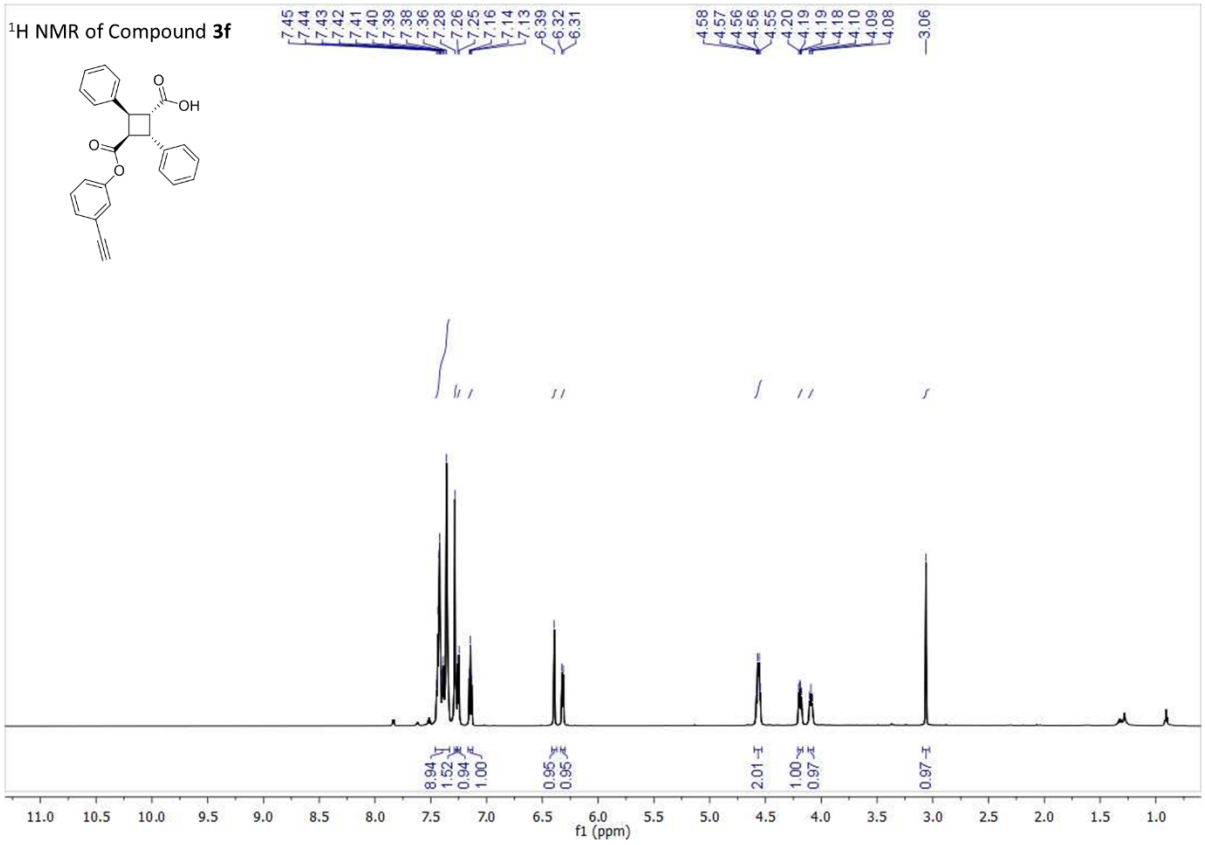
^{1}H NMR of Compound **3e**



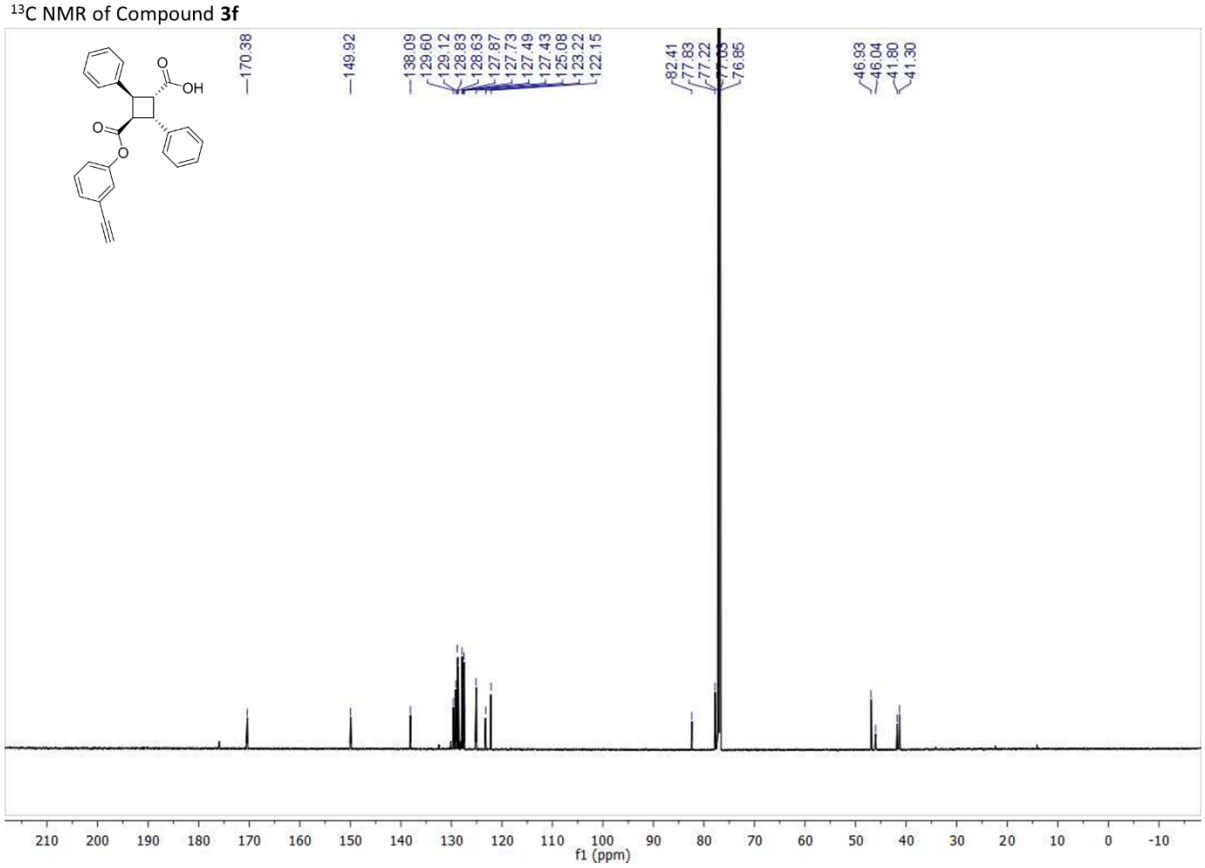
^{13}C NMR of Compound **3e**



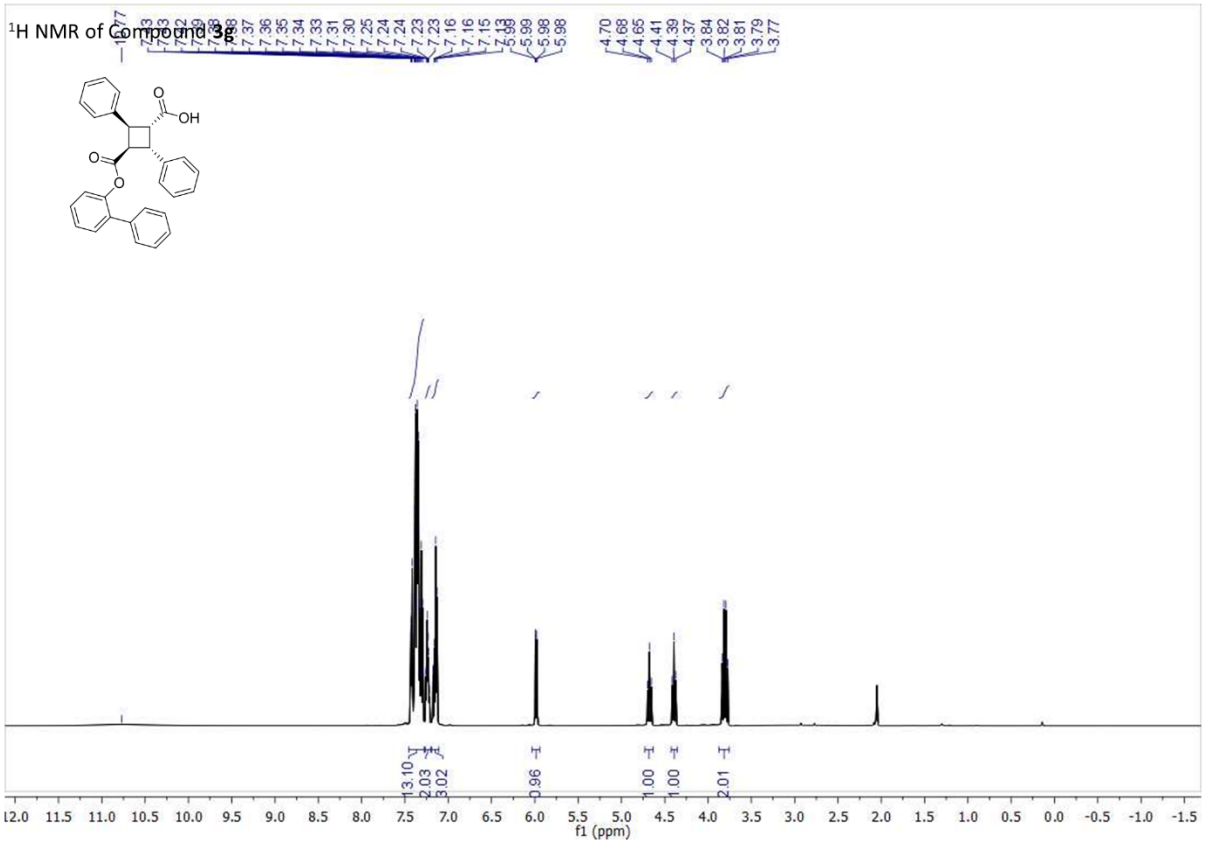
^{1}H NMR of Compound **3f**



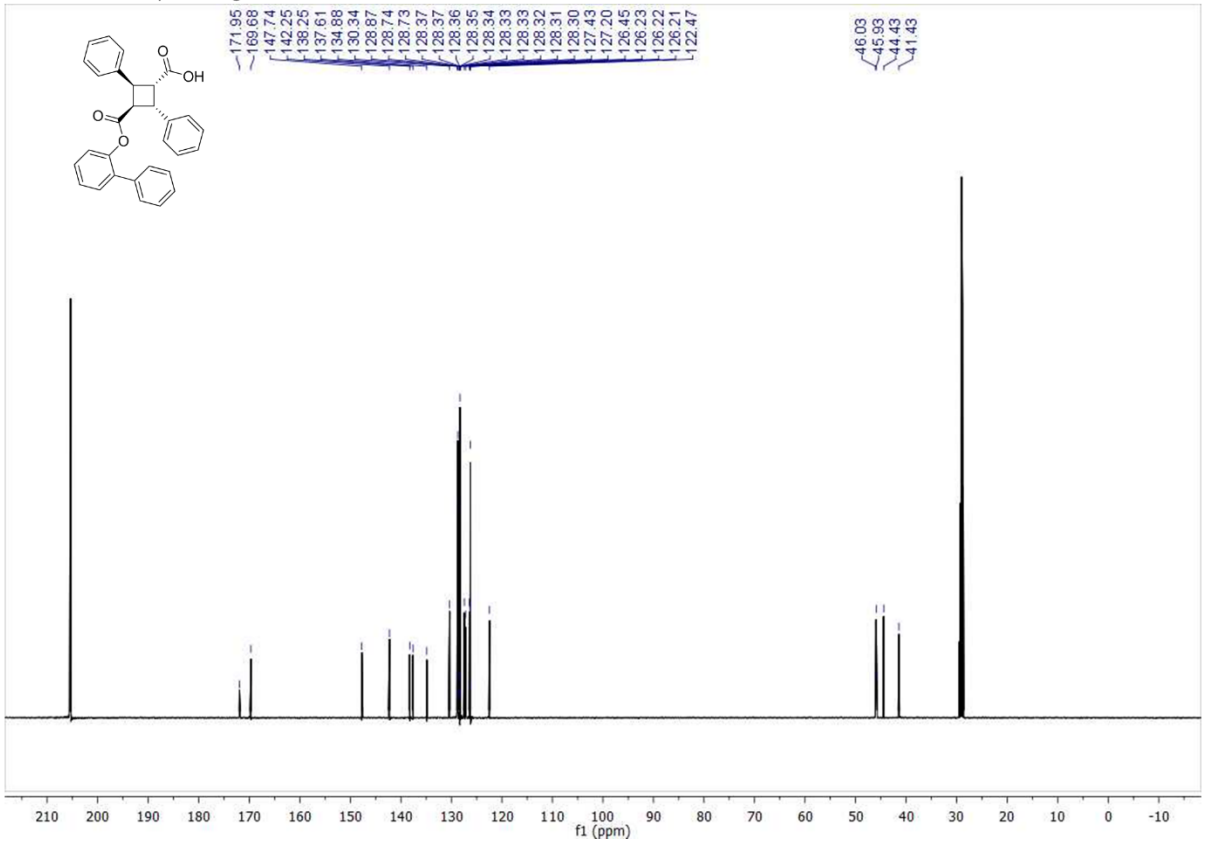
^{13}C NMR of Compound **3f**



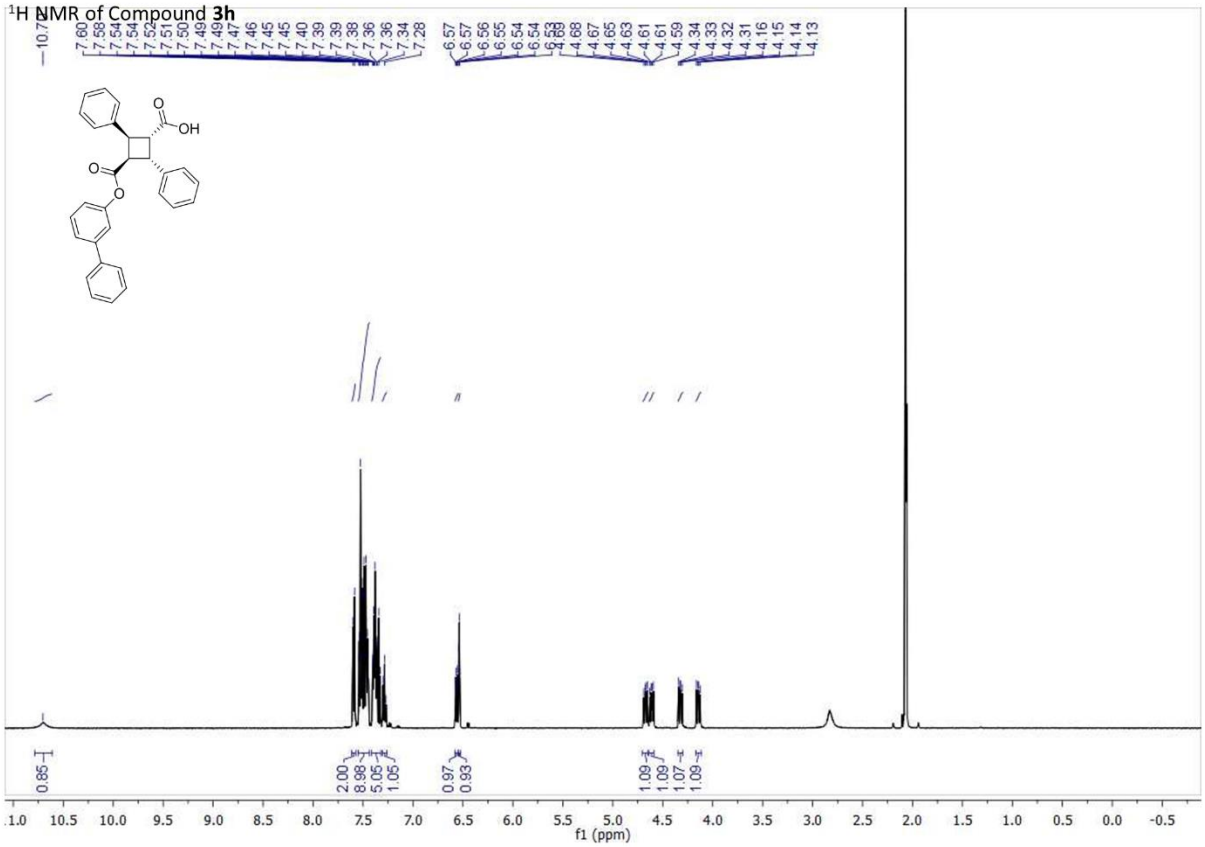
^{1}H NMR of Compound **3g**



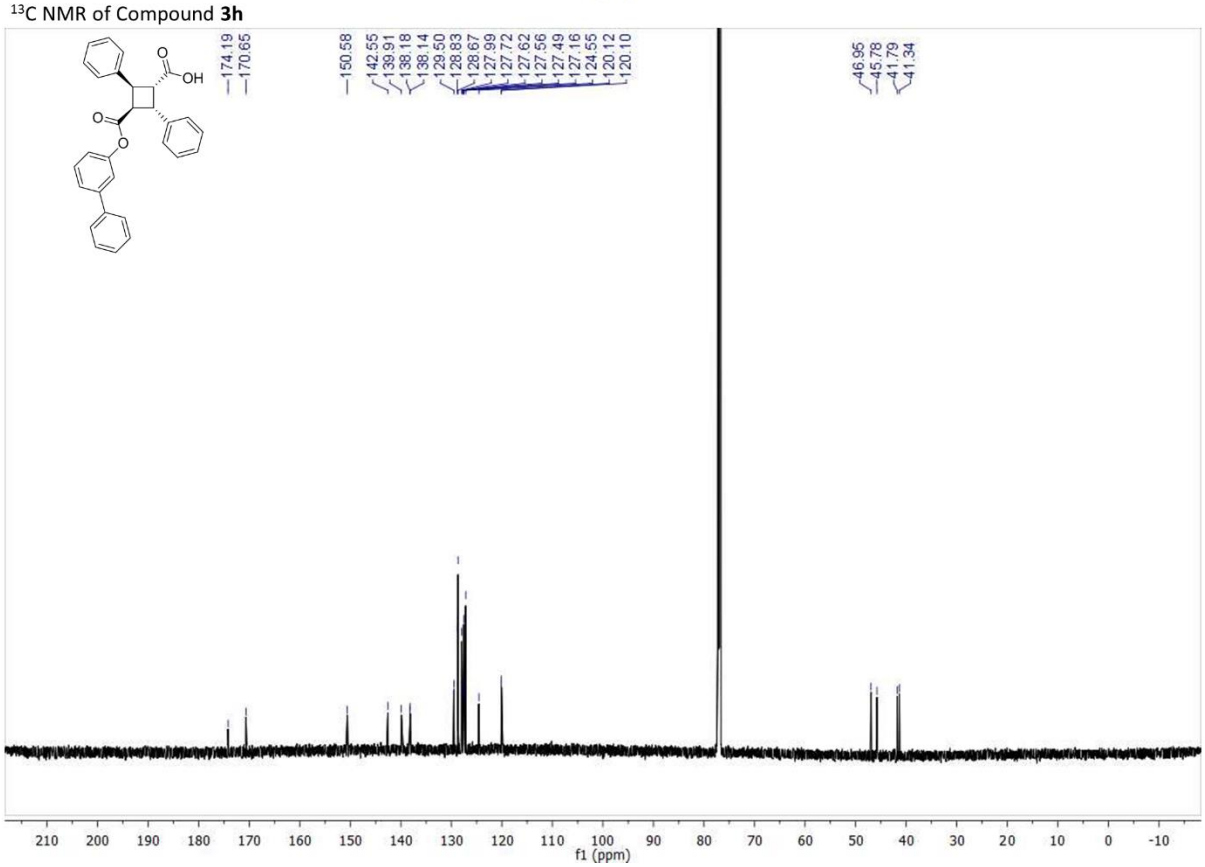
^{13}C NMR of Compound **3g**



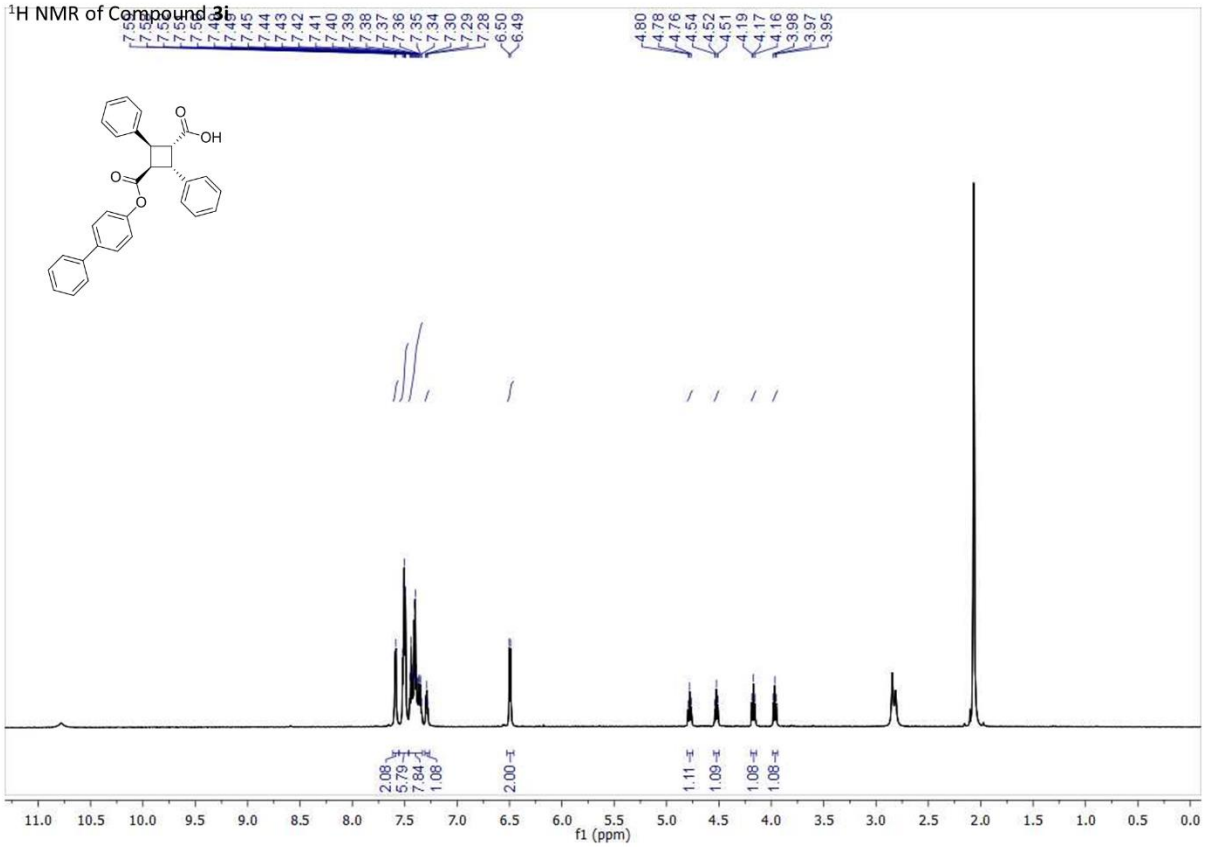
^{1}H NMR of Compound **3h**



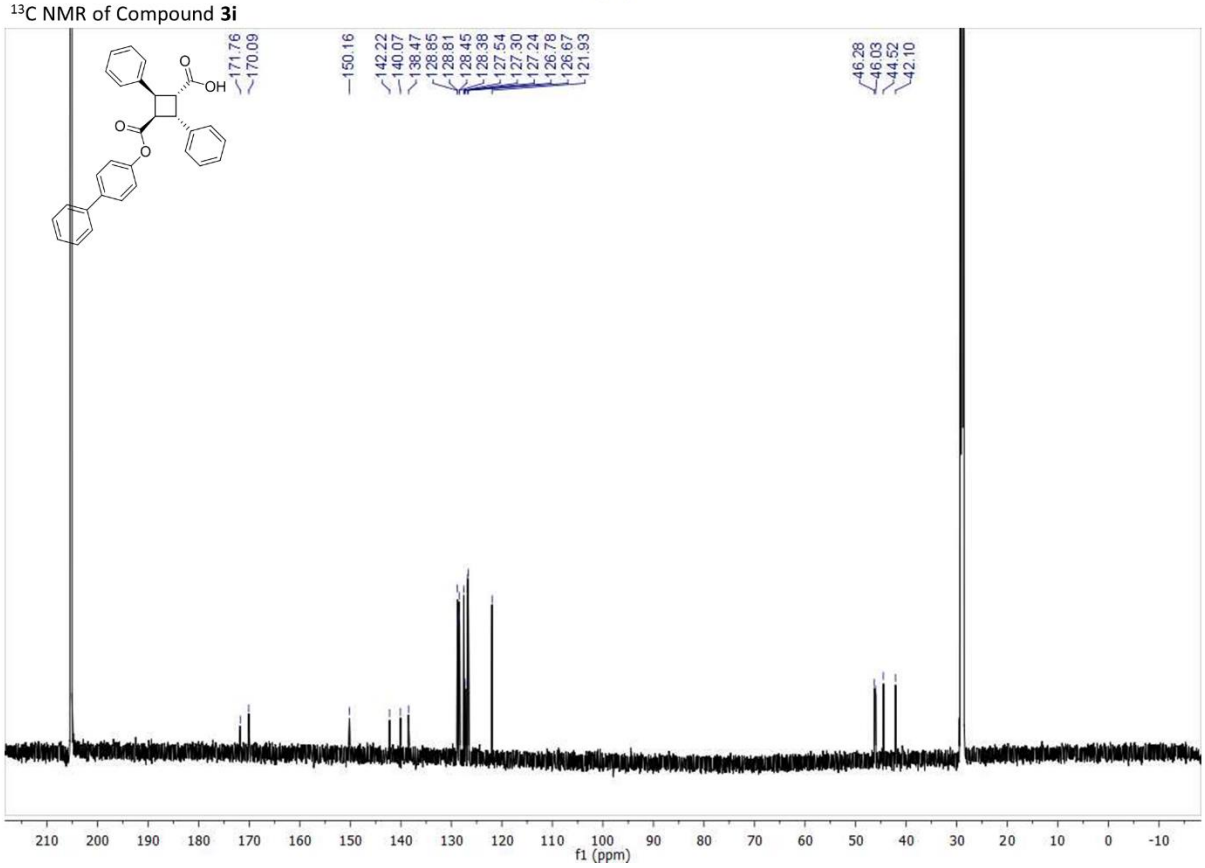
^{13}C NMR of Compound **3h**



^{1}H NMR of Compound **3i**



^{13}C NMR of Compound **3i**



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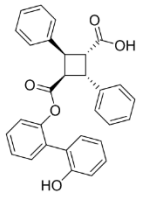
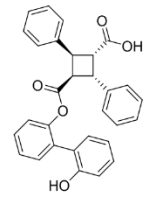


^{1}H NMR of Compound **3j**



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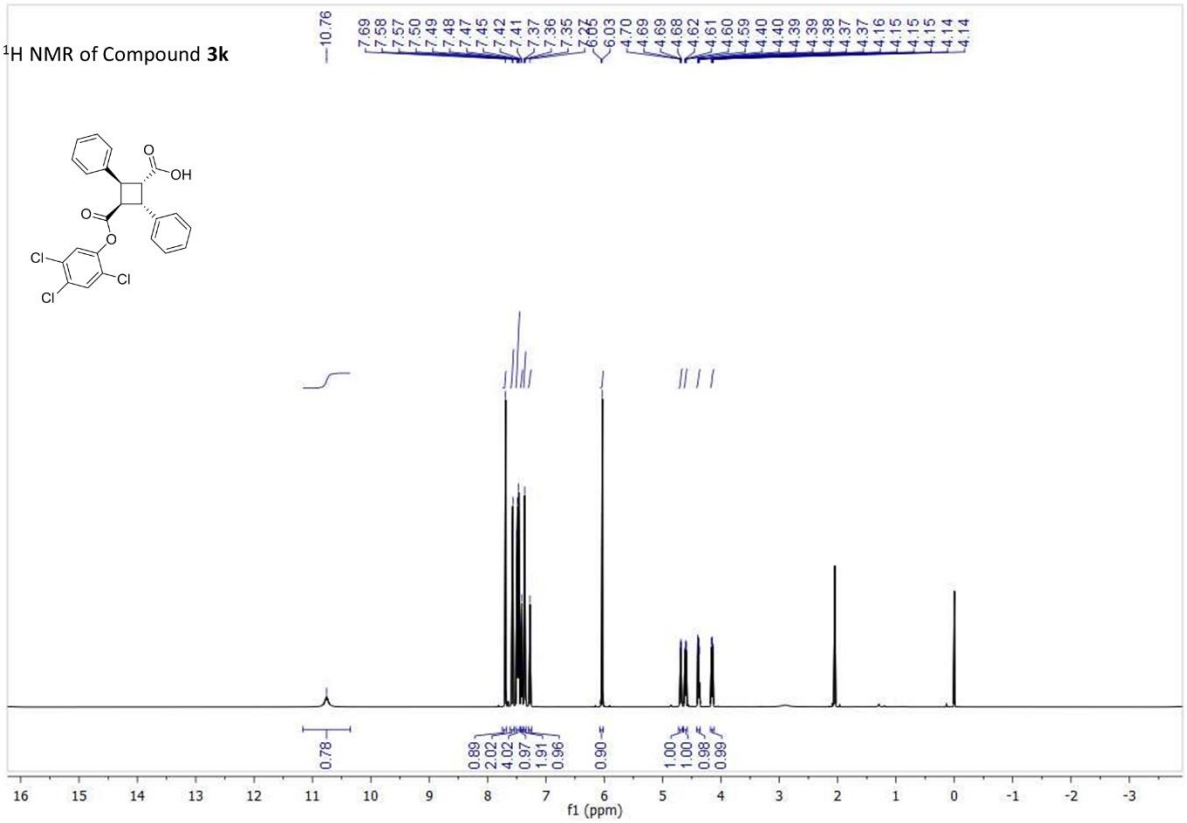

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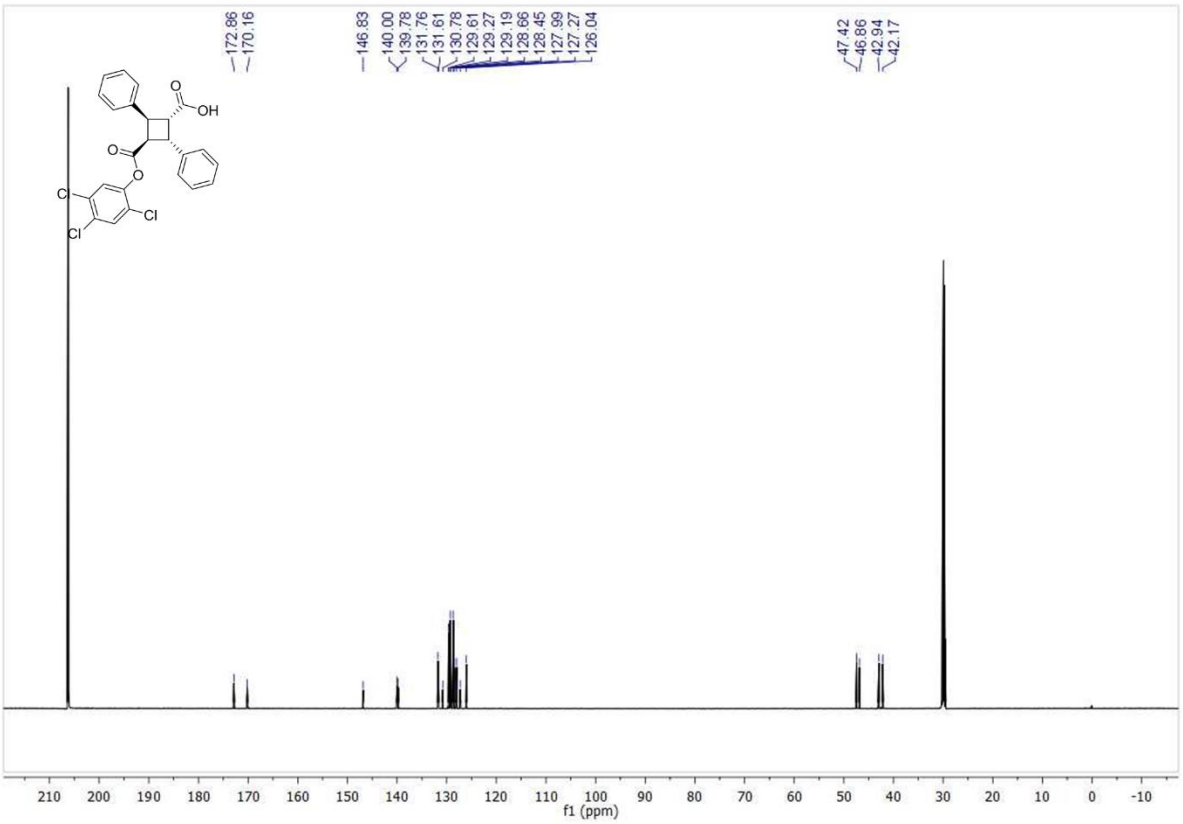
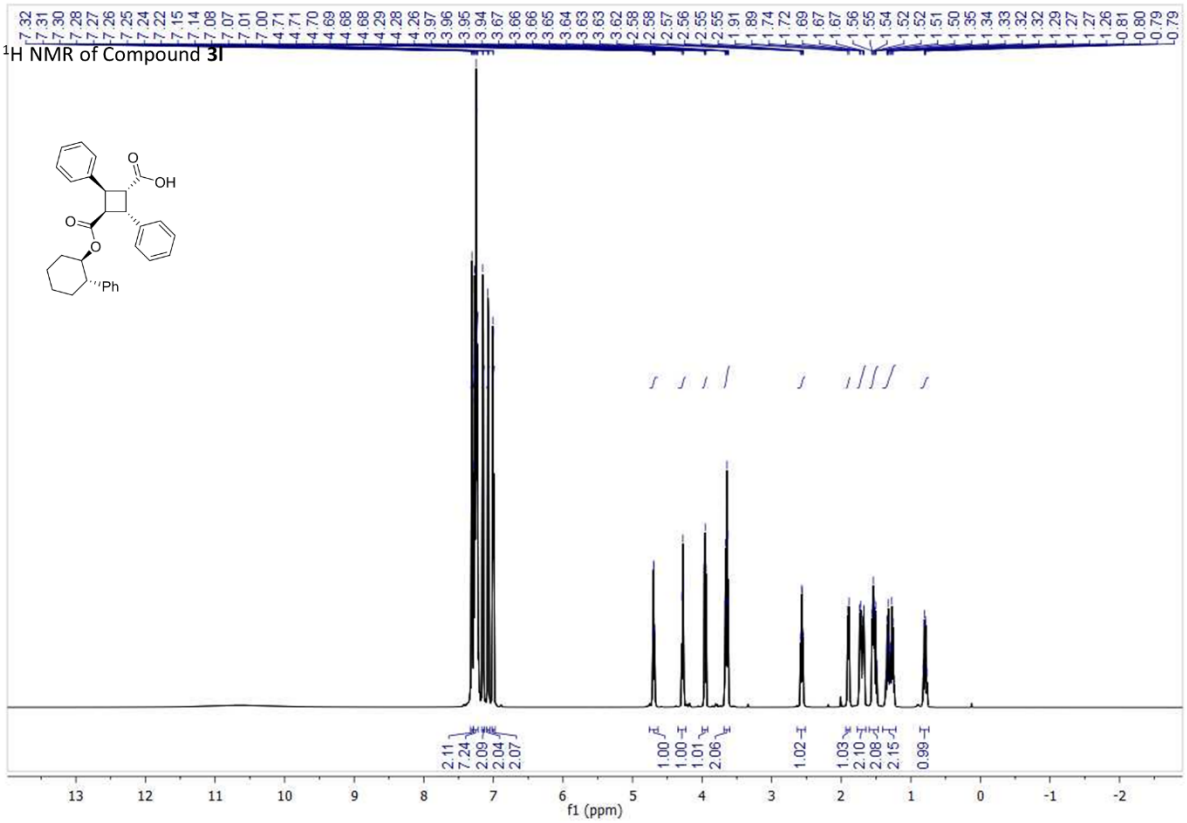


^{1}H NMR of Compound **3l**



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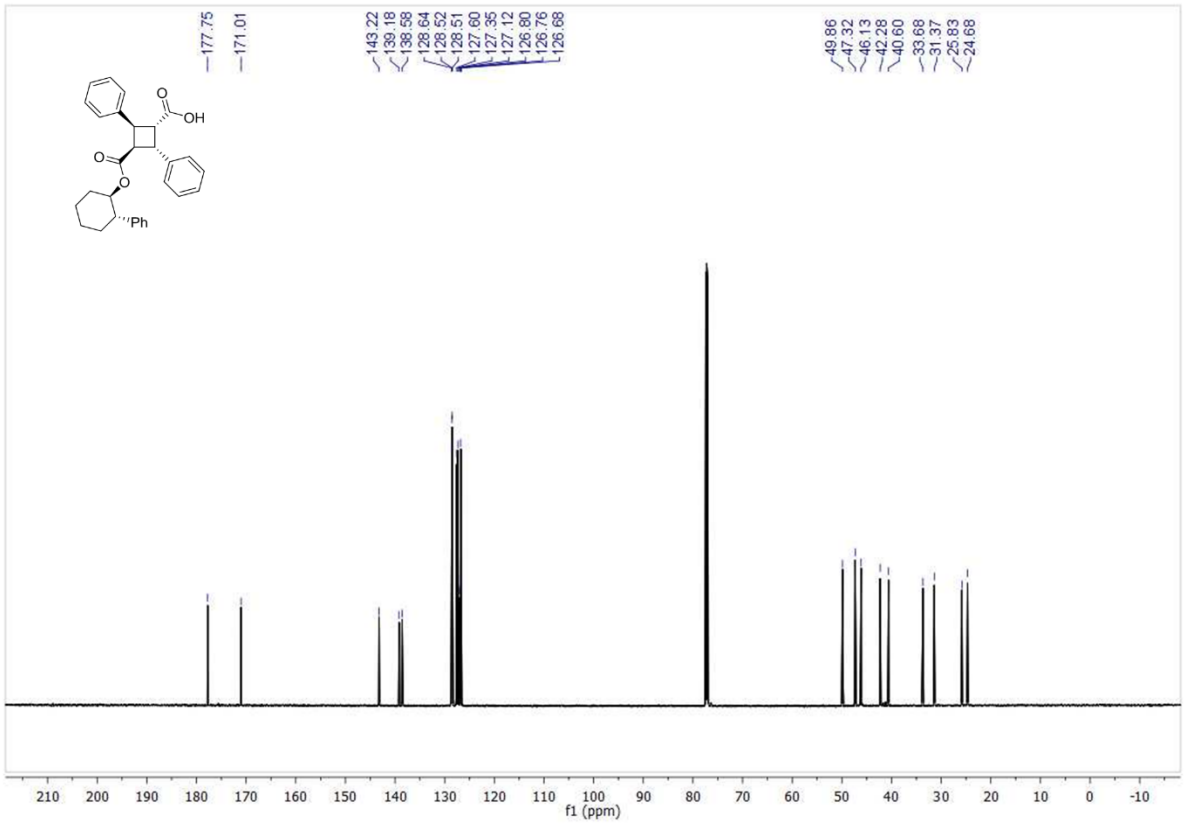
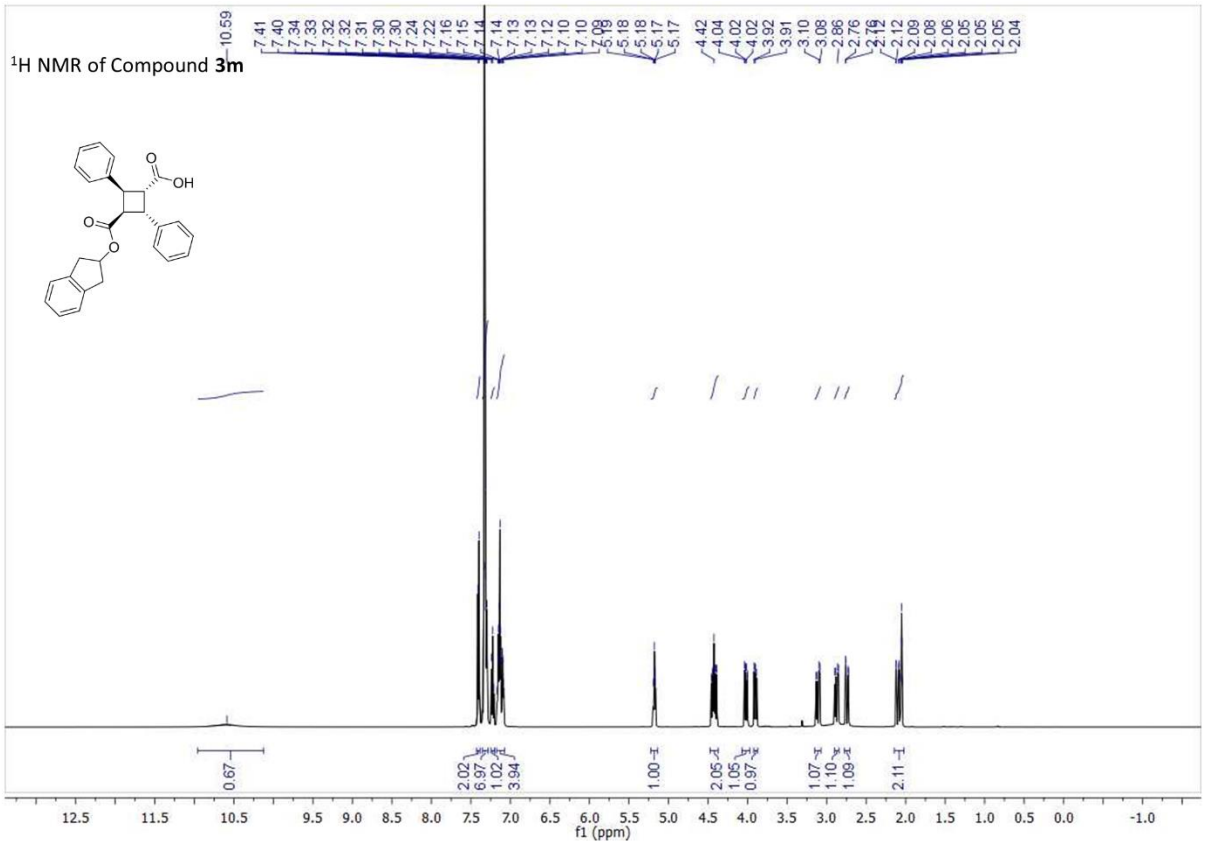
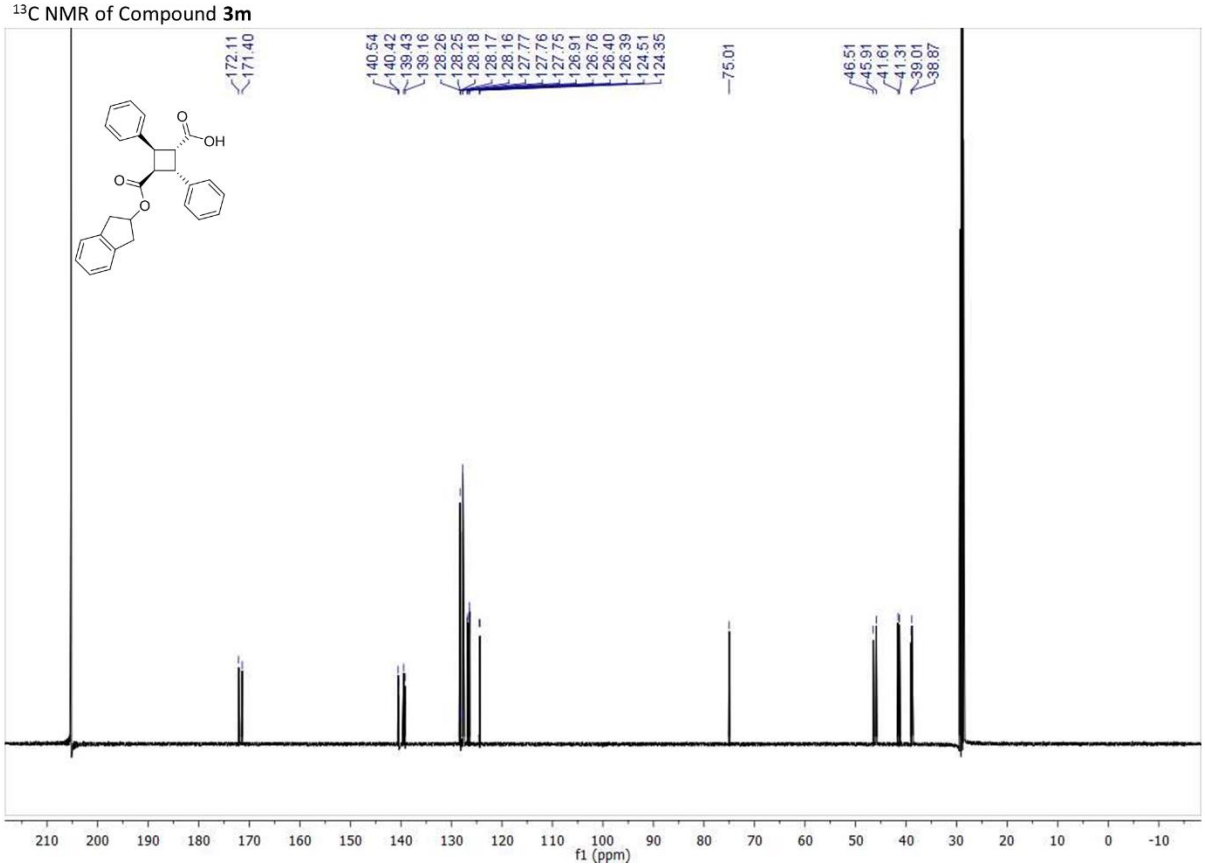


^{1}H NMR of Compound **3m**



^{13}C NMR of Compound **3m**



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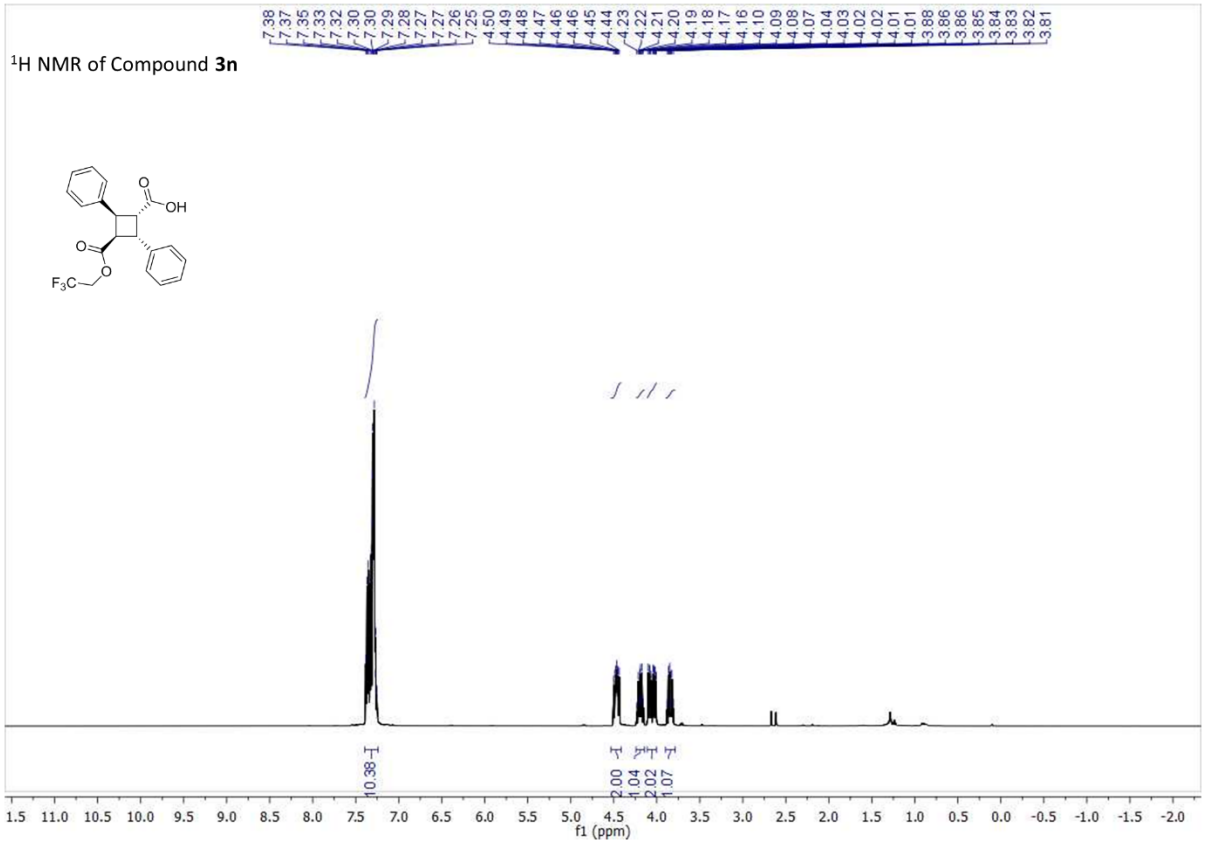
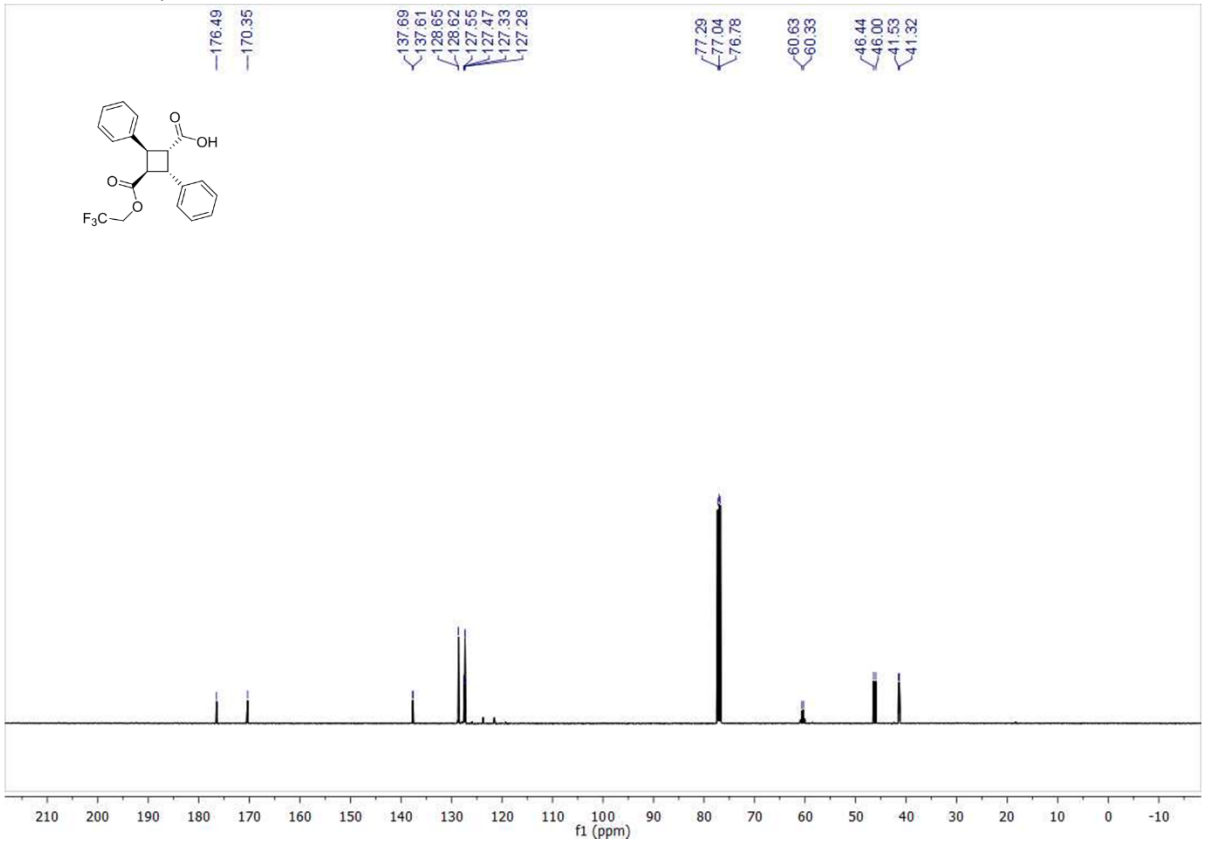
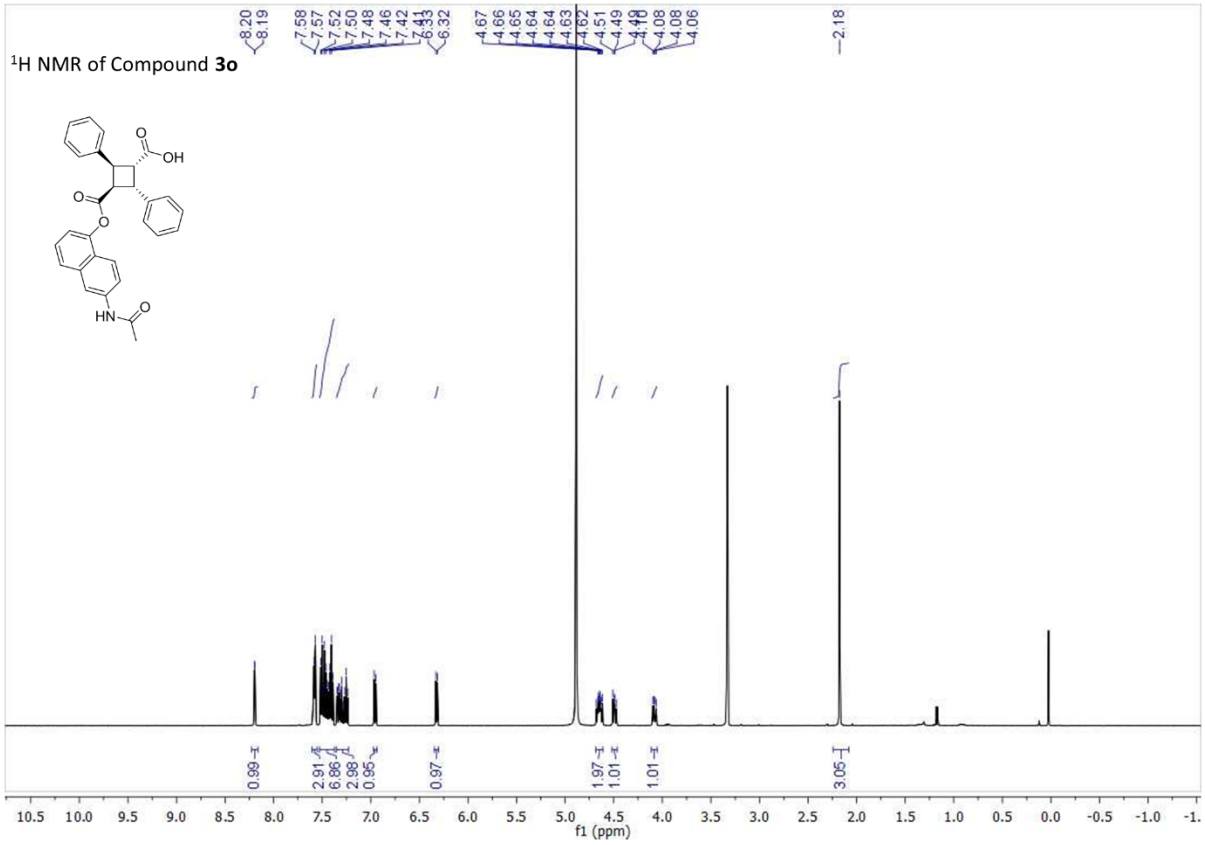


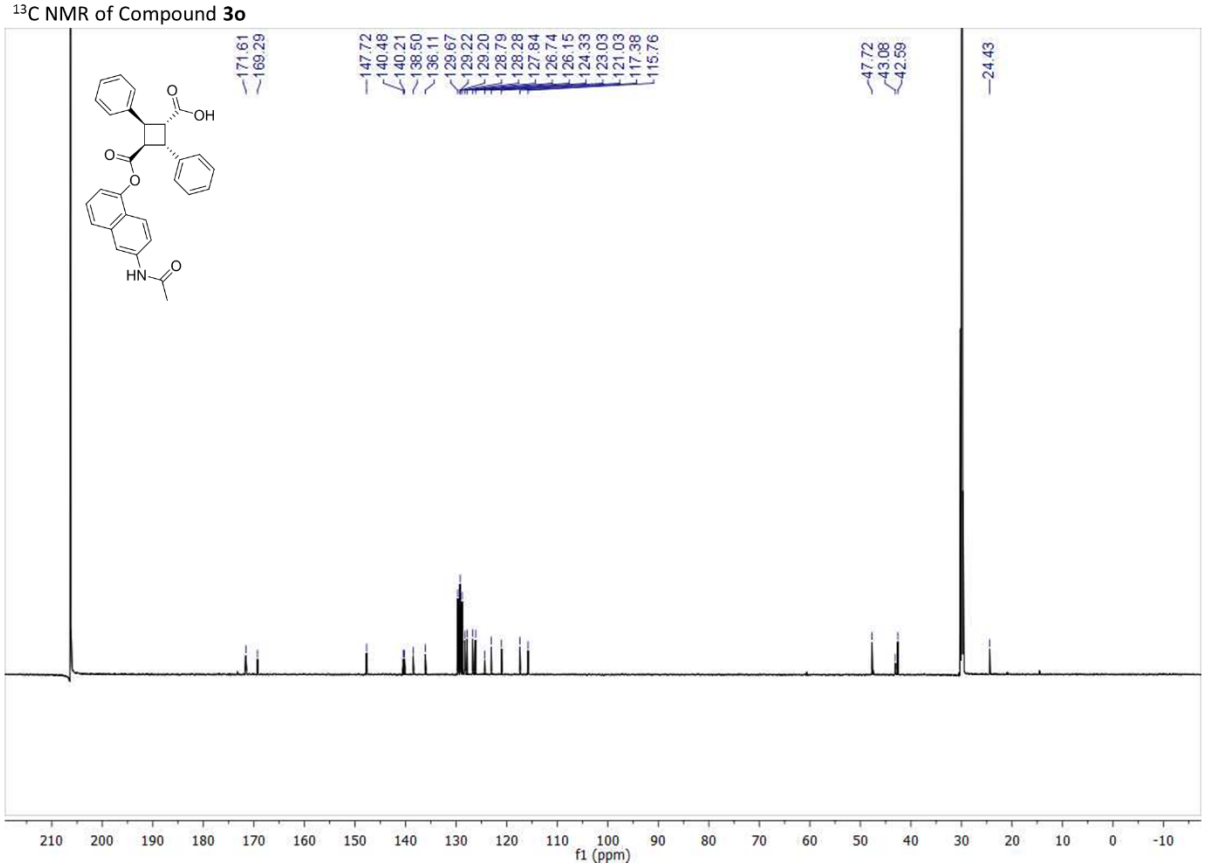
^{13}C NMR of Compound **3n**



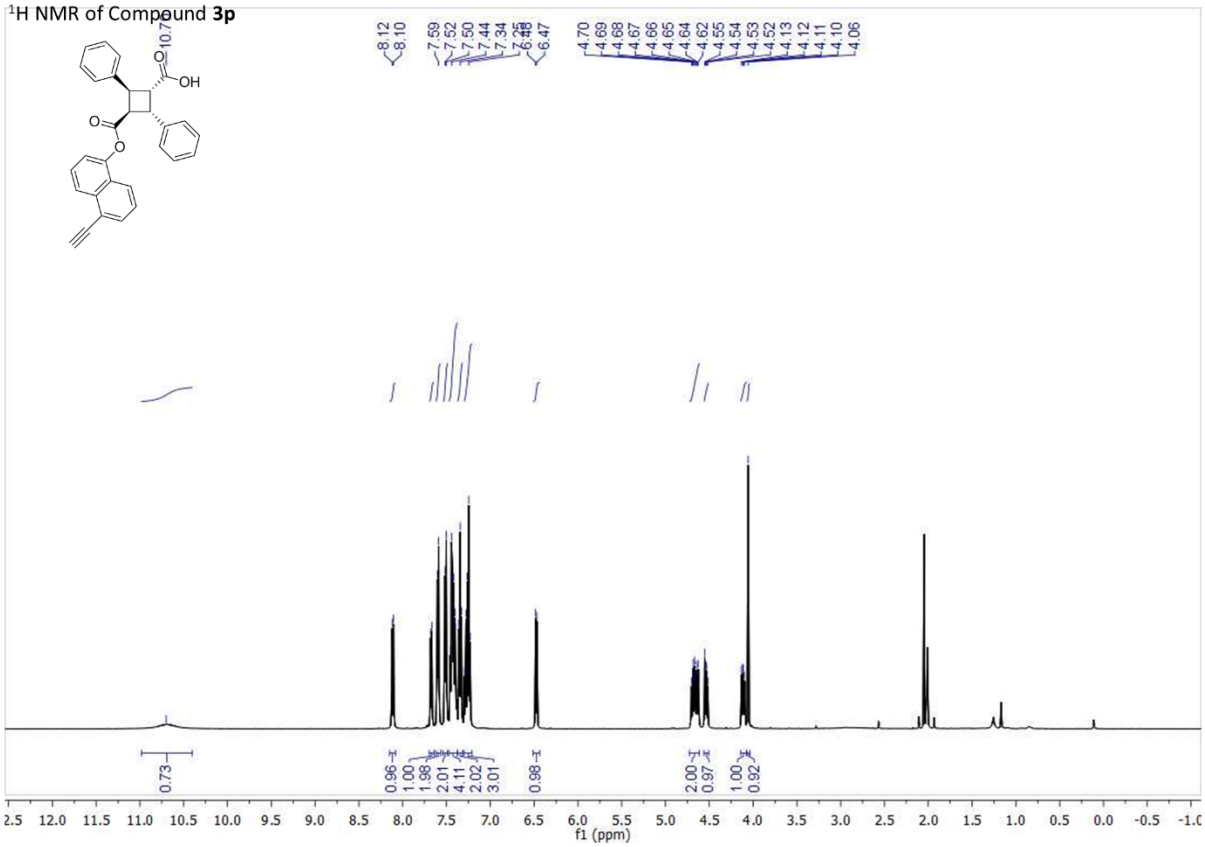
^{1}H NMR of Compound **3o**



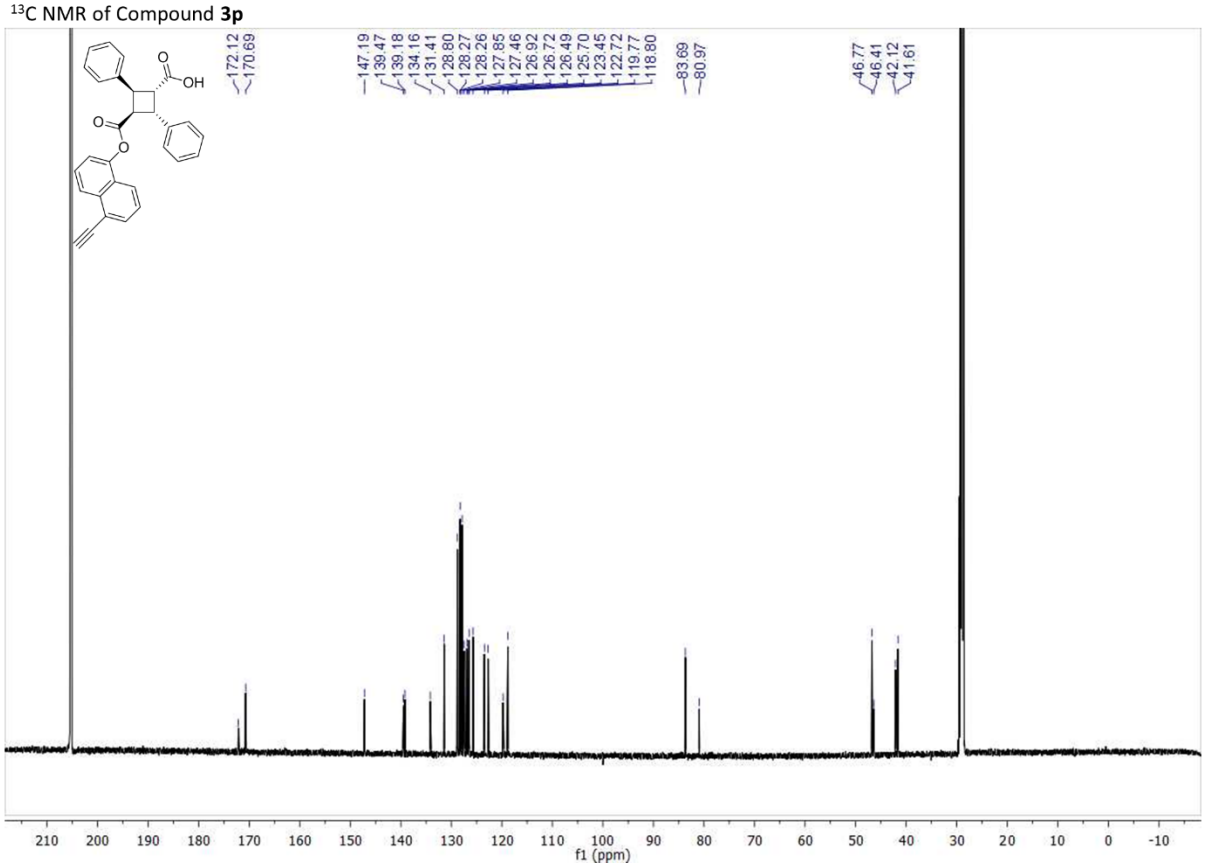
^{13}C NMR of Compound **3o**



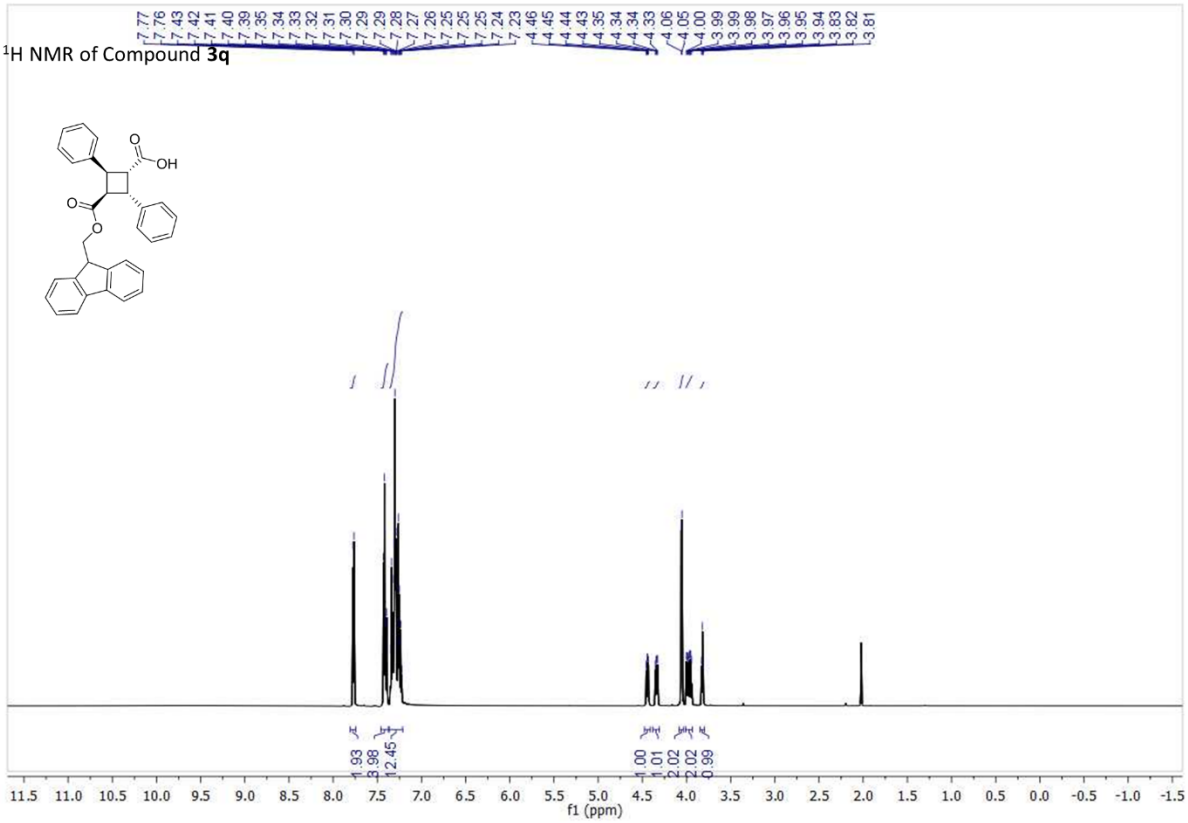
^{1}H NMR of Compound **3p**



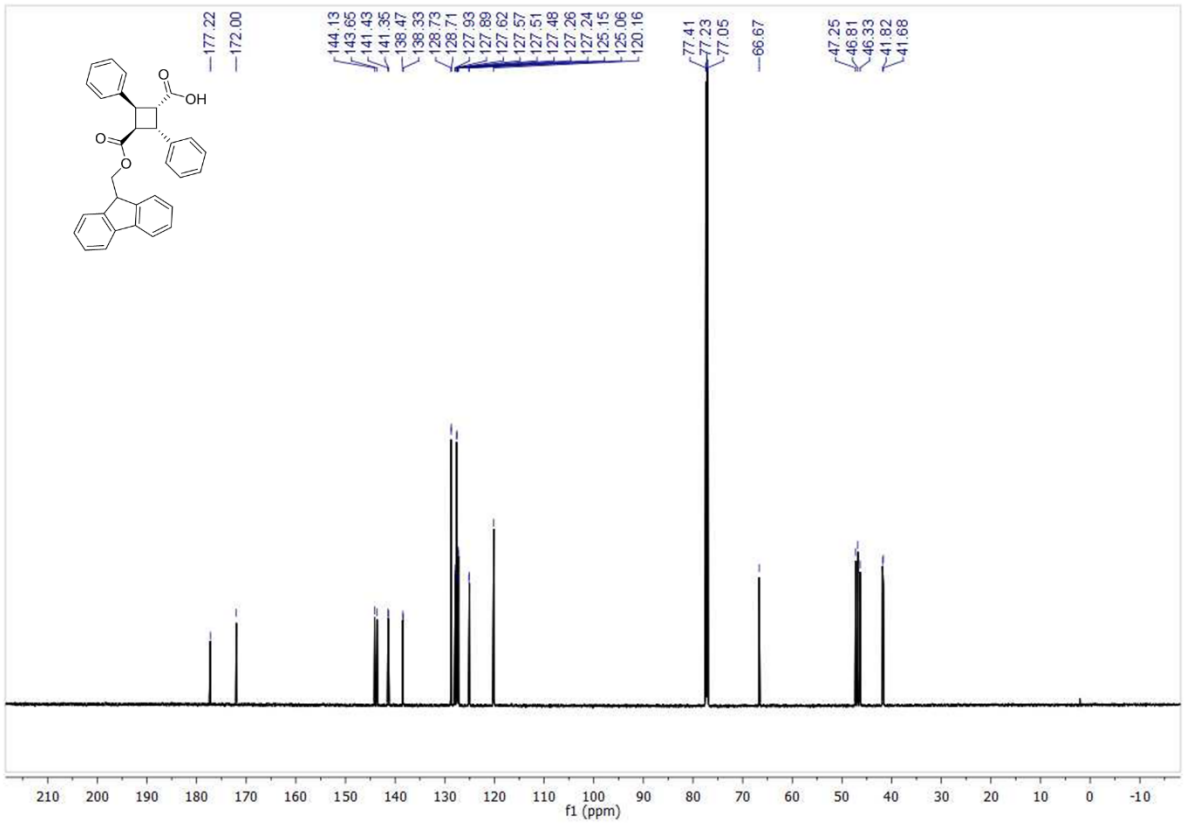
^{13}C NMR of Compound **3p**



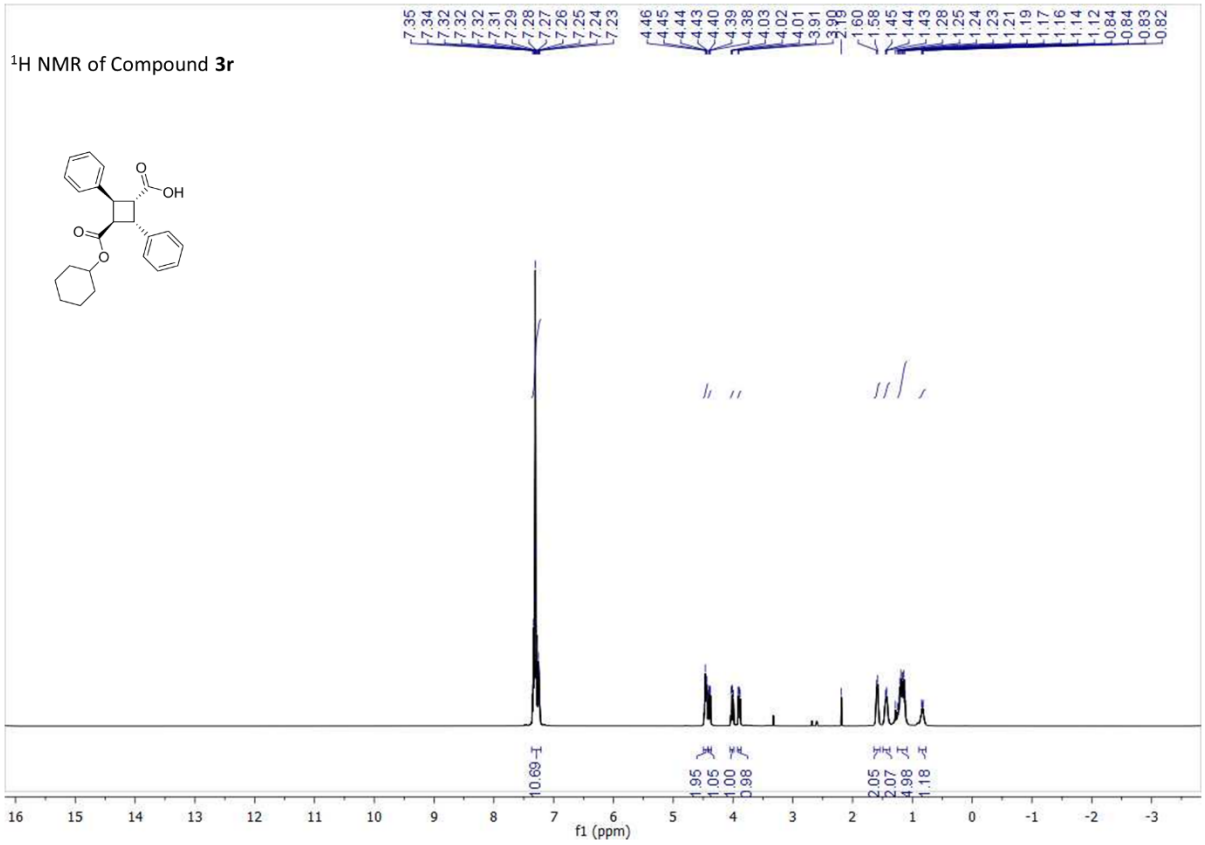
^{1}H NMR of Compound **3q**



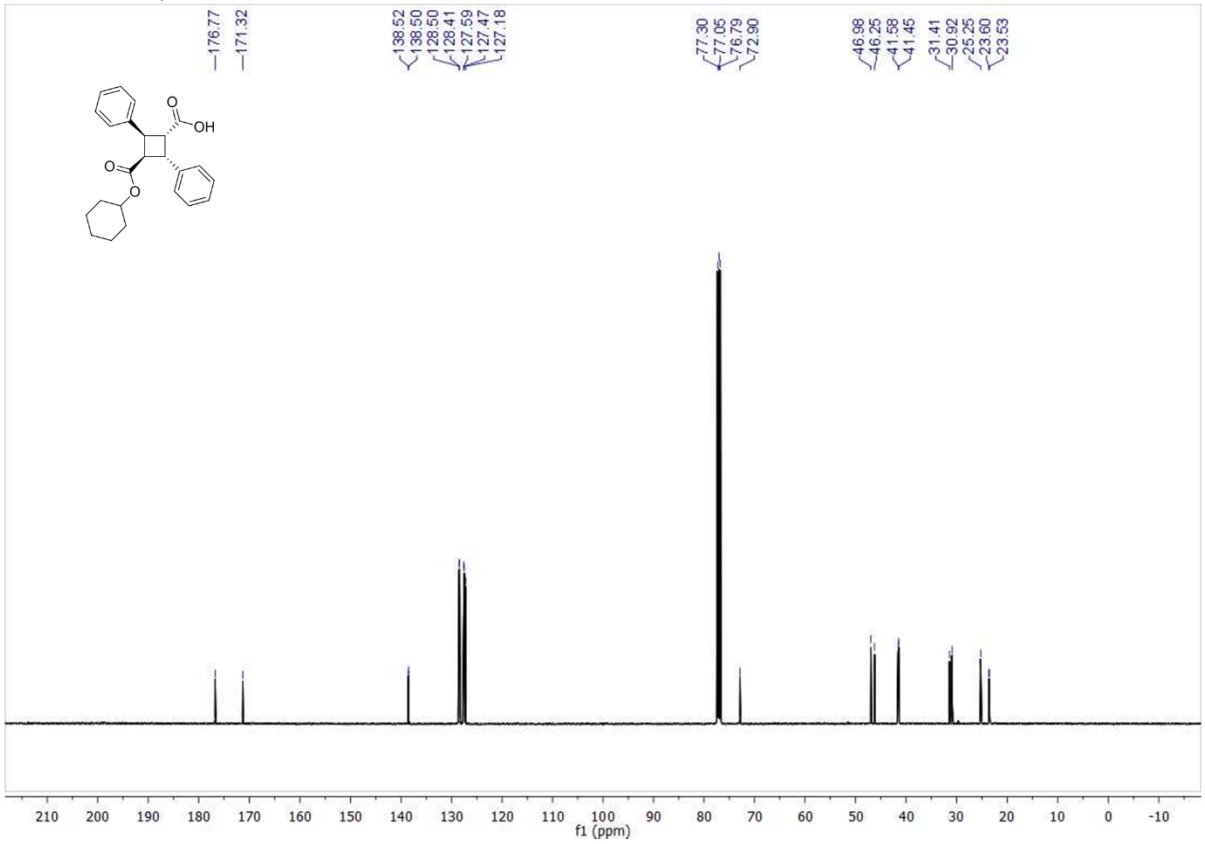
^{13}C NMR of Compound **3q**



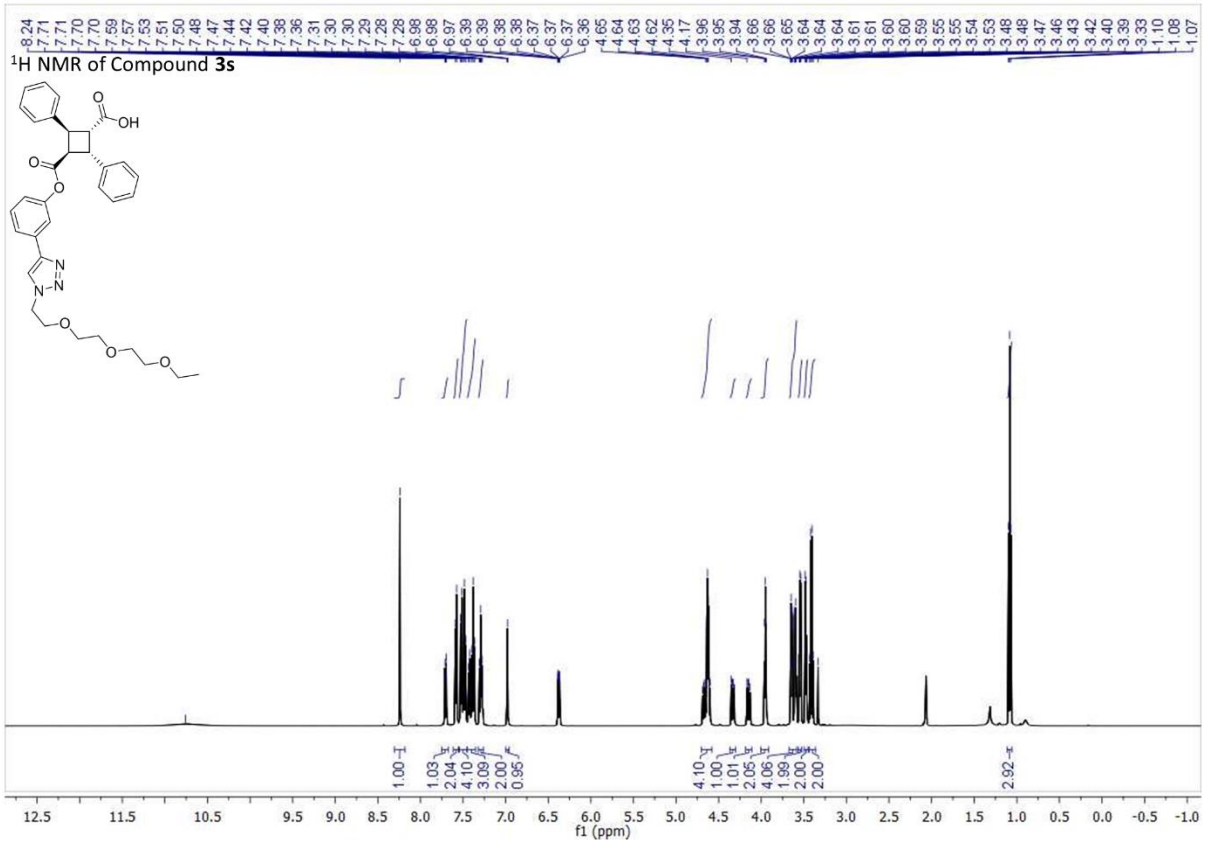
^{1}H NMR of Compound **3r**



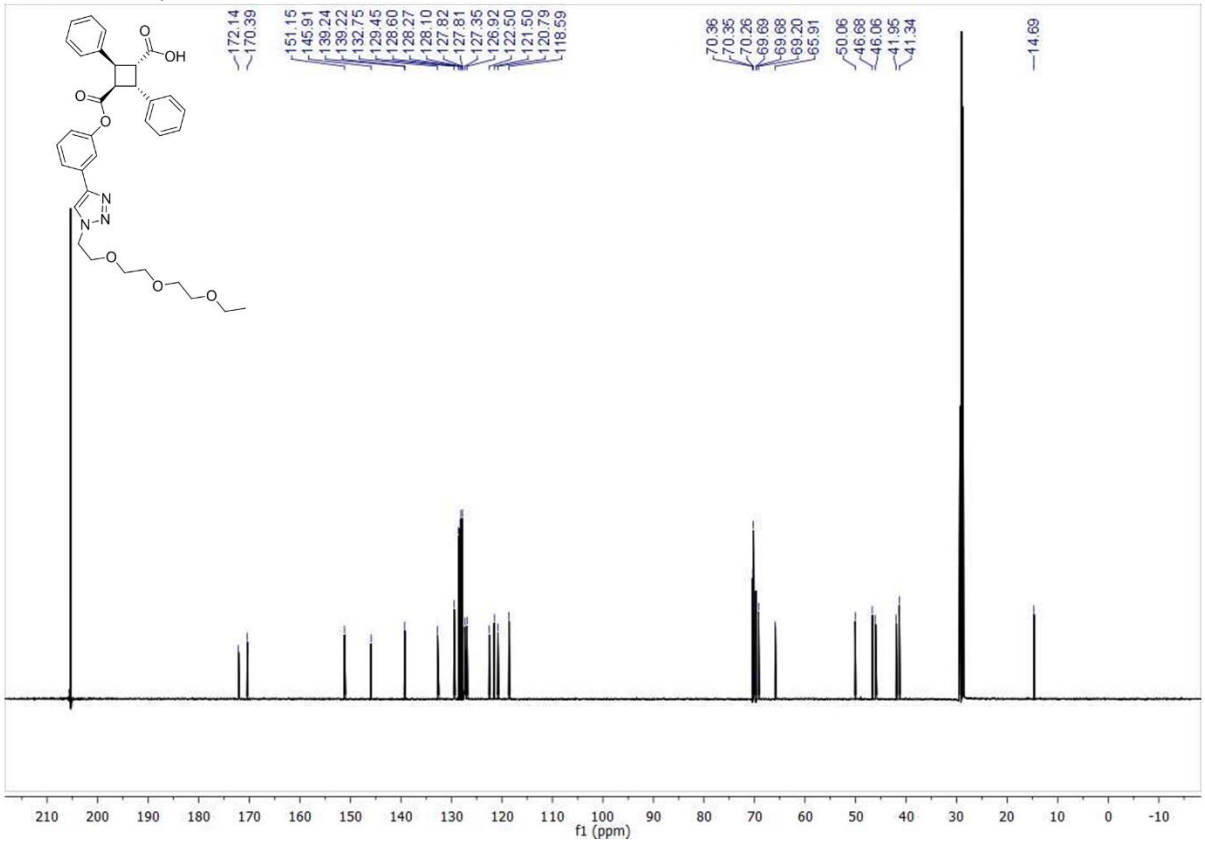
^{13}C NMR of Compound **3r**



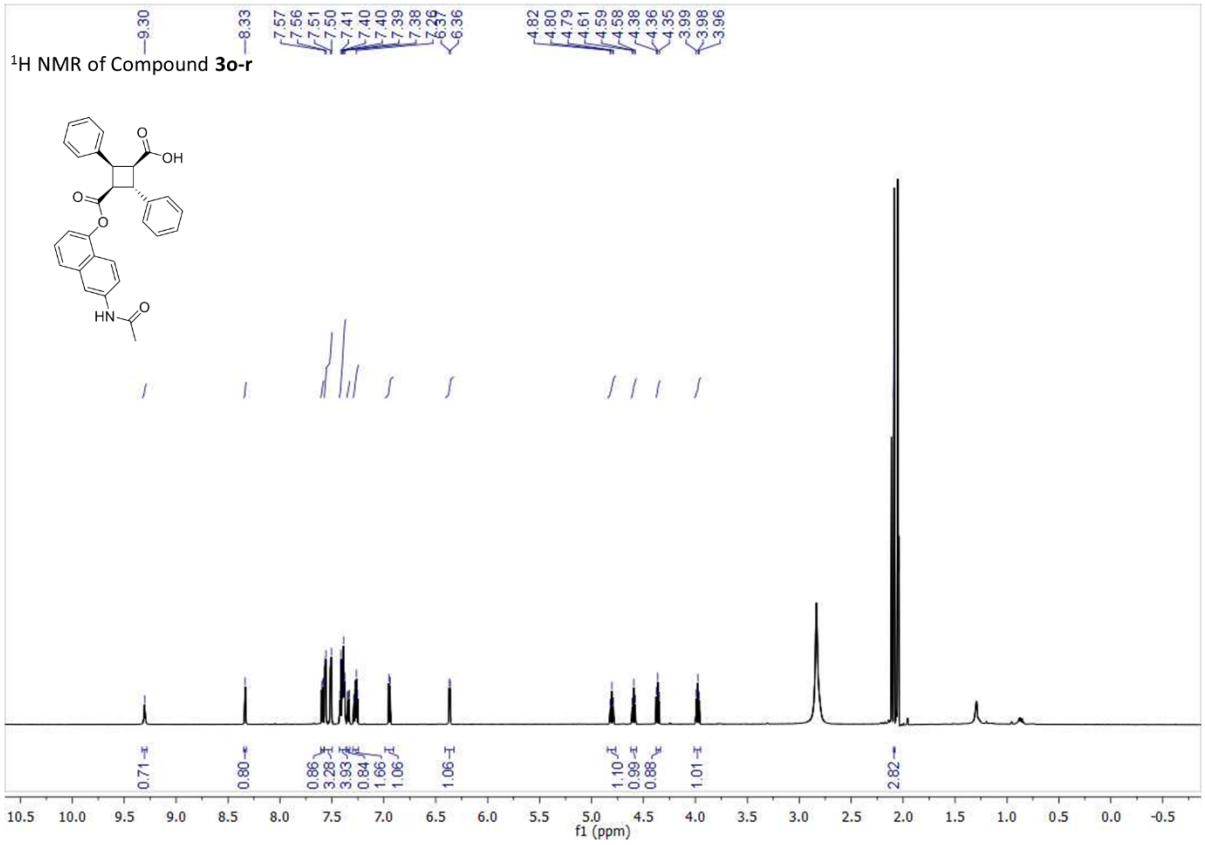
^{1}H NMR of Compound **3s**



^{13}C NMR of Compound **3s**



^{1}H NMR of Compound **3o-r**



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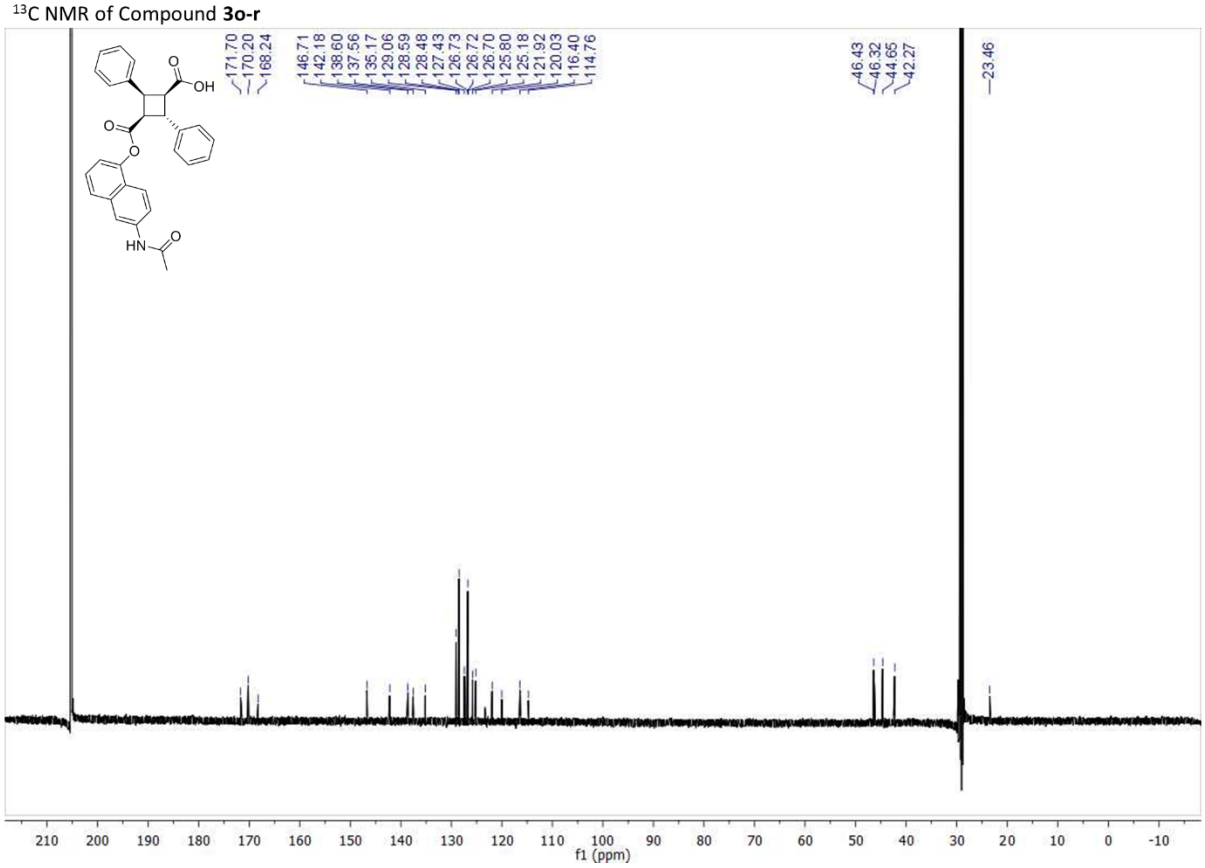
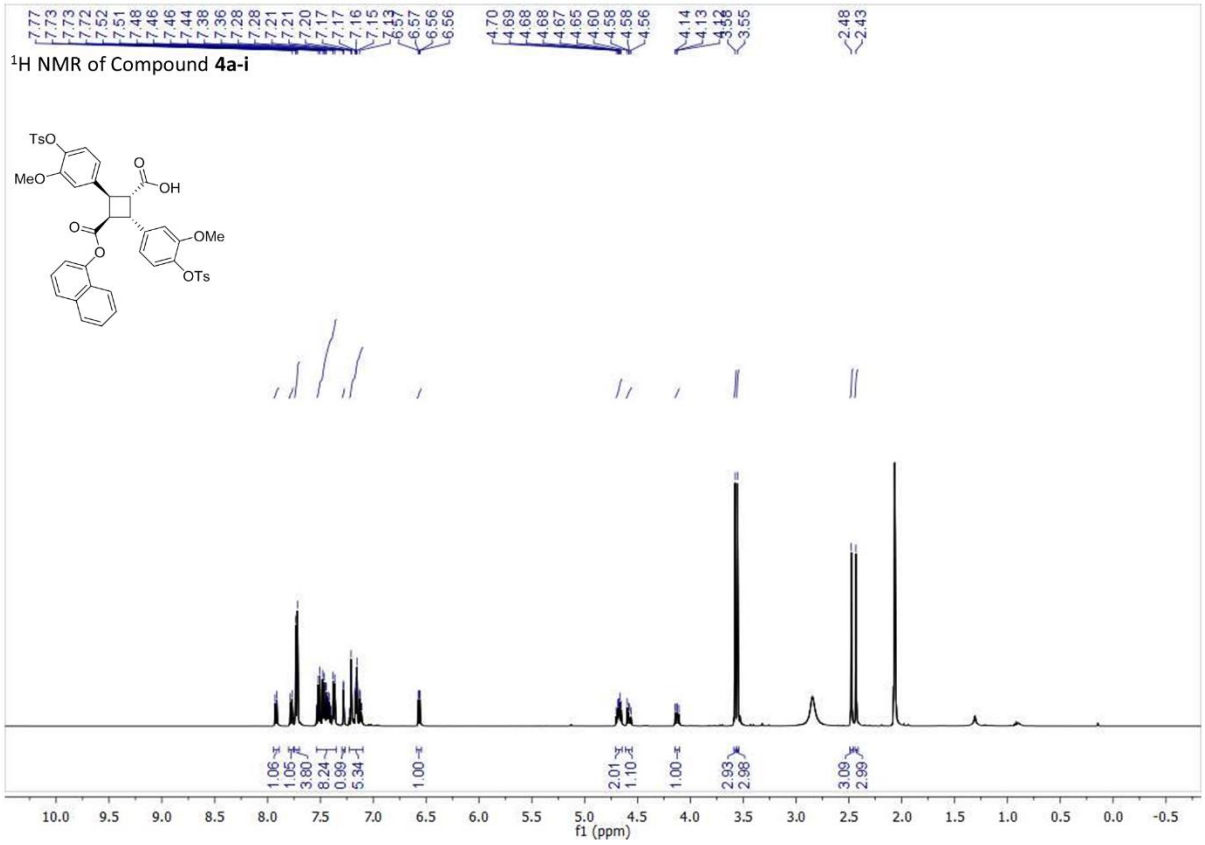
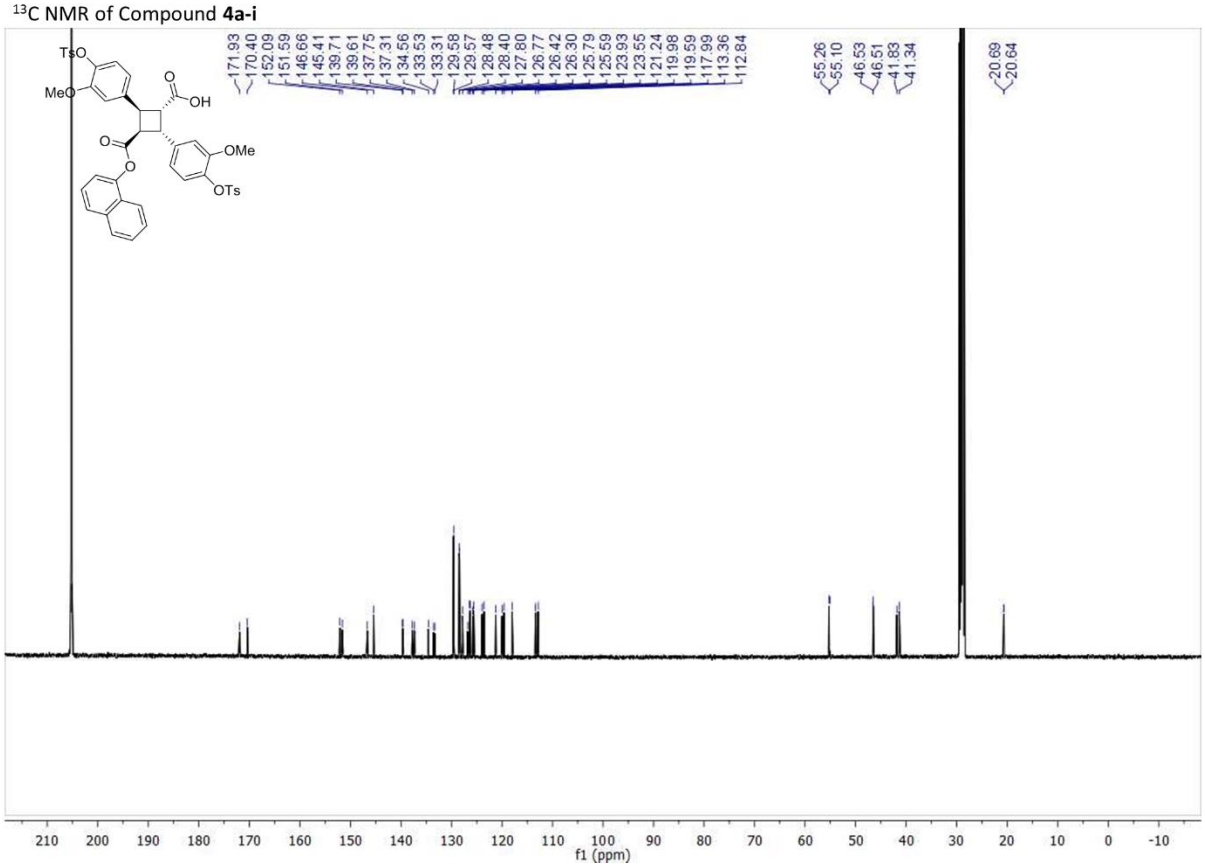


^{1}H NMR of Compound **4a-i**



^{13}C NMR of Compound **4a-i**



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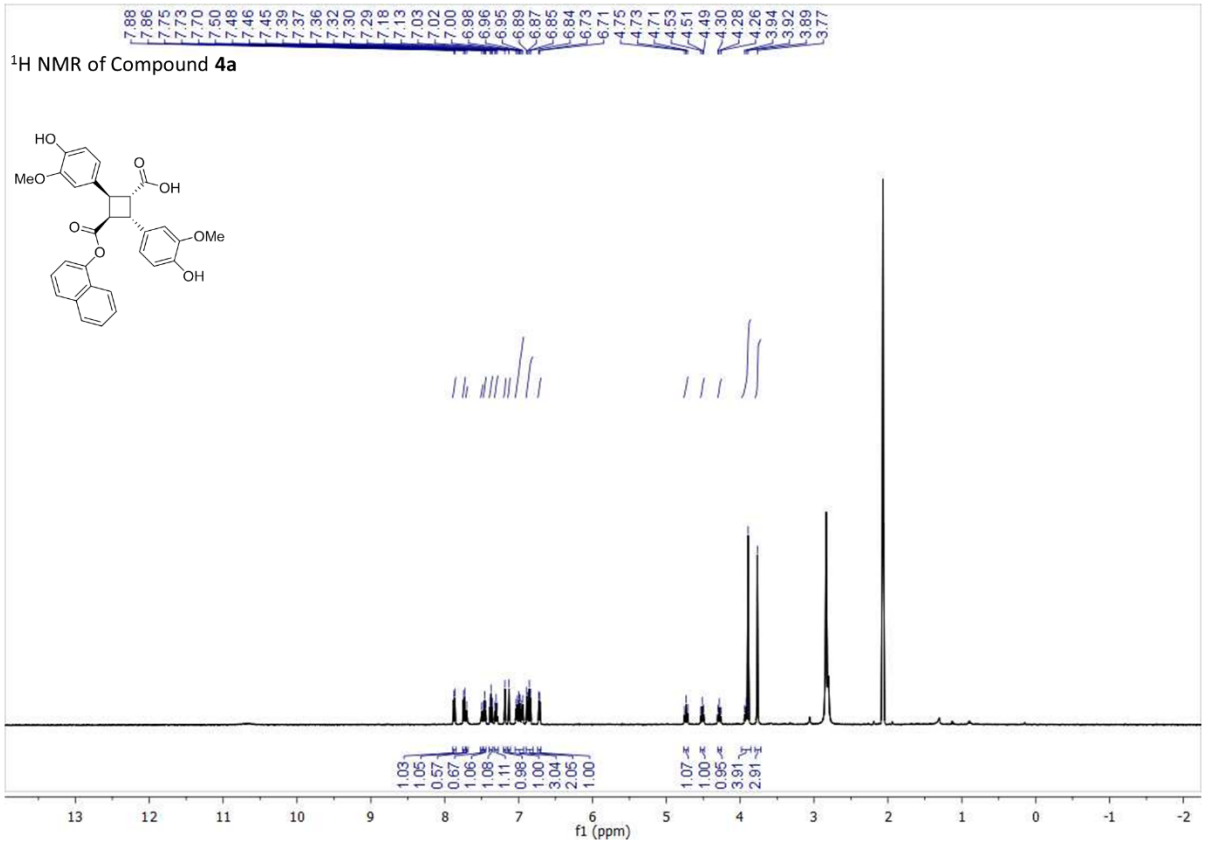

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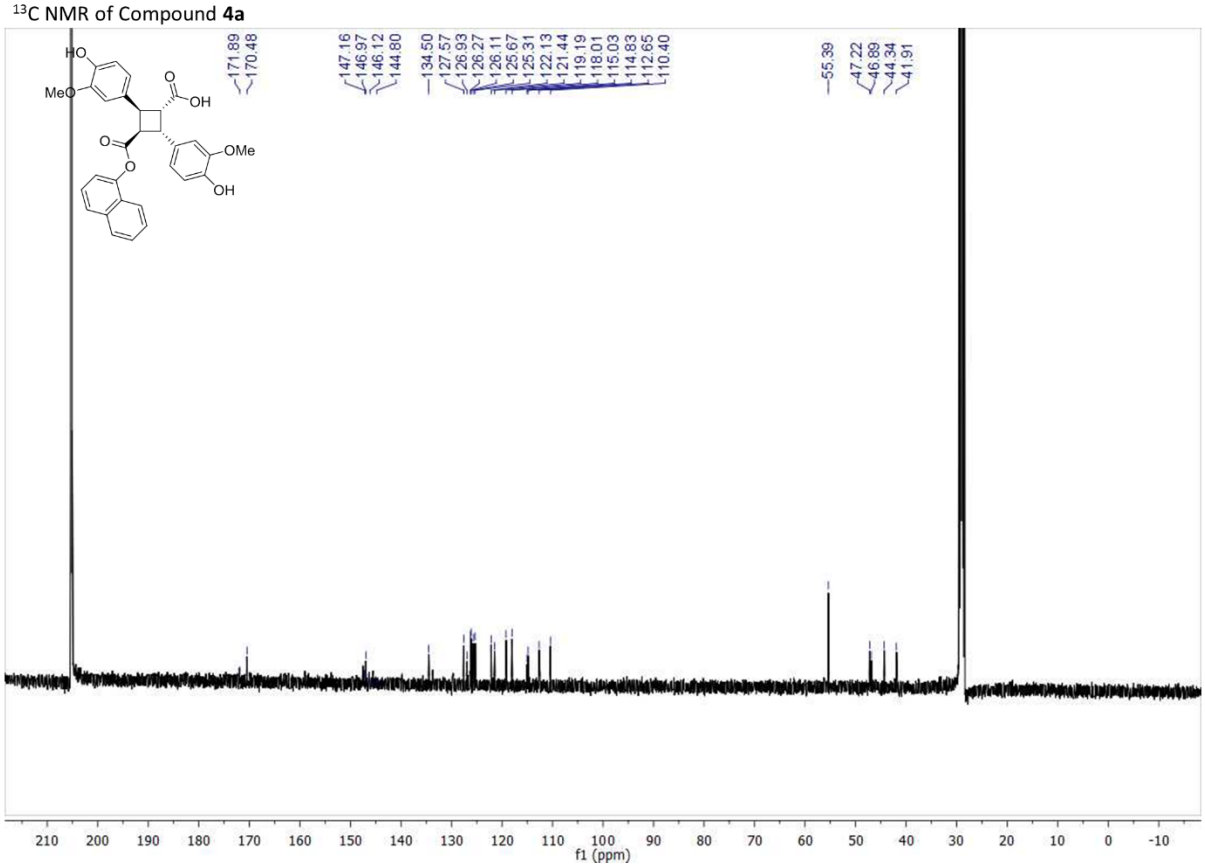
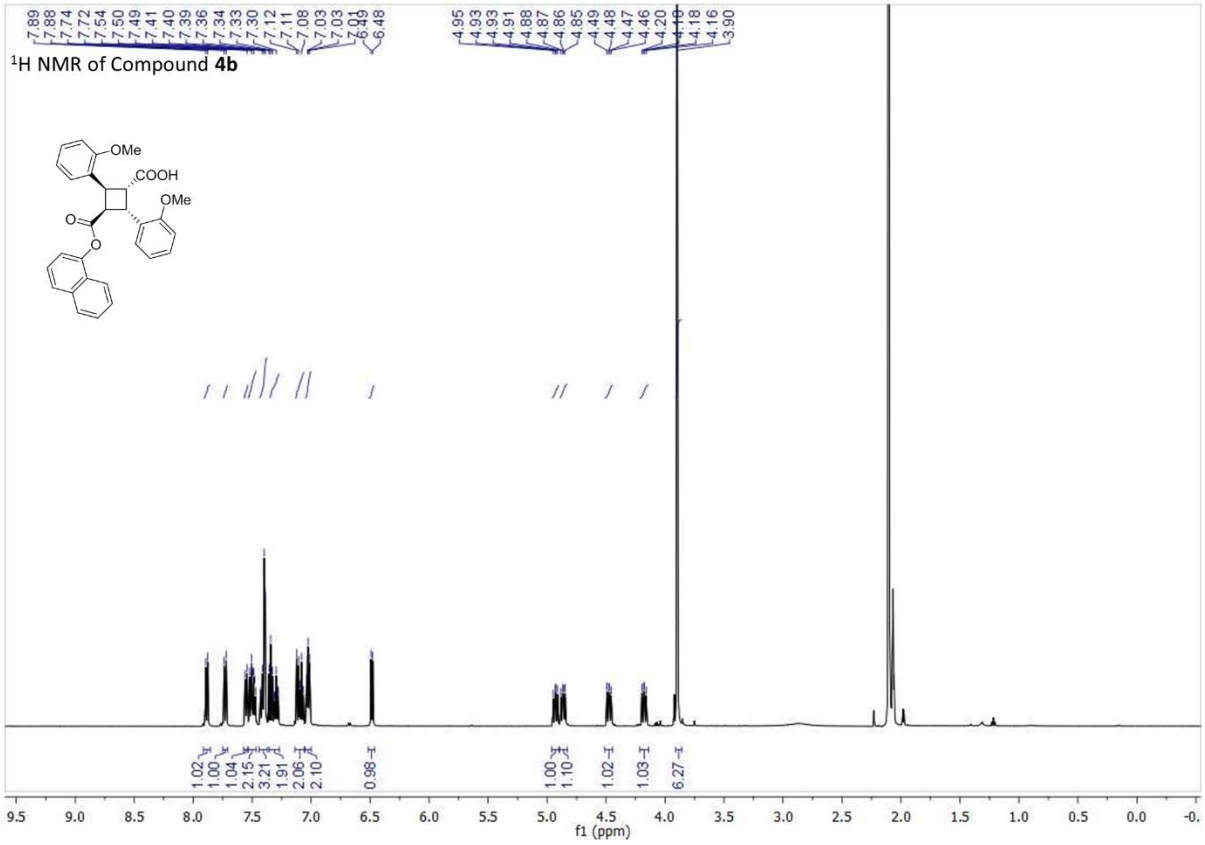
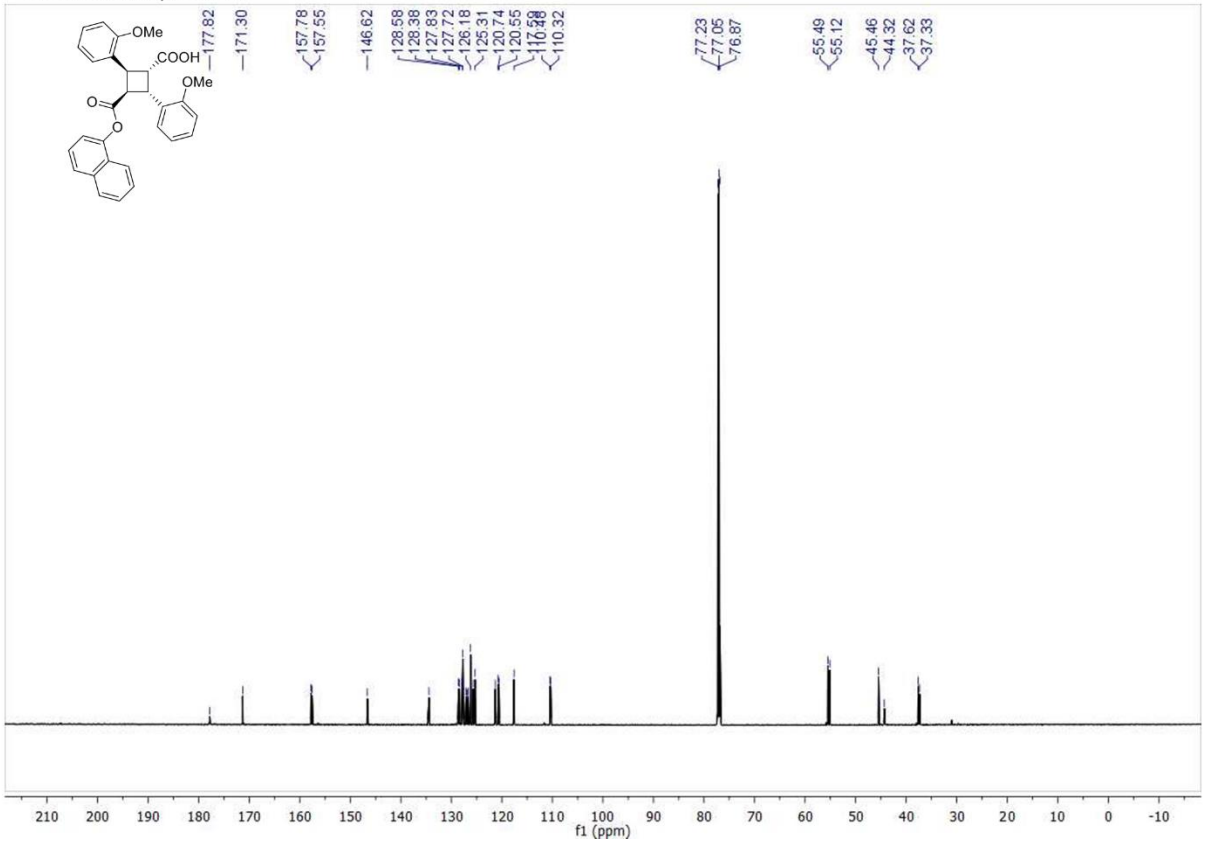


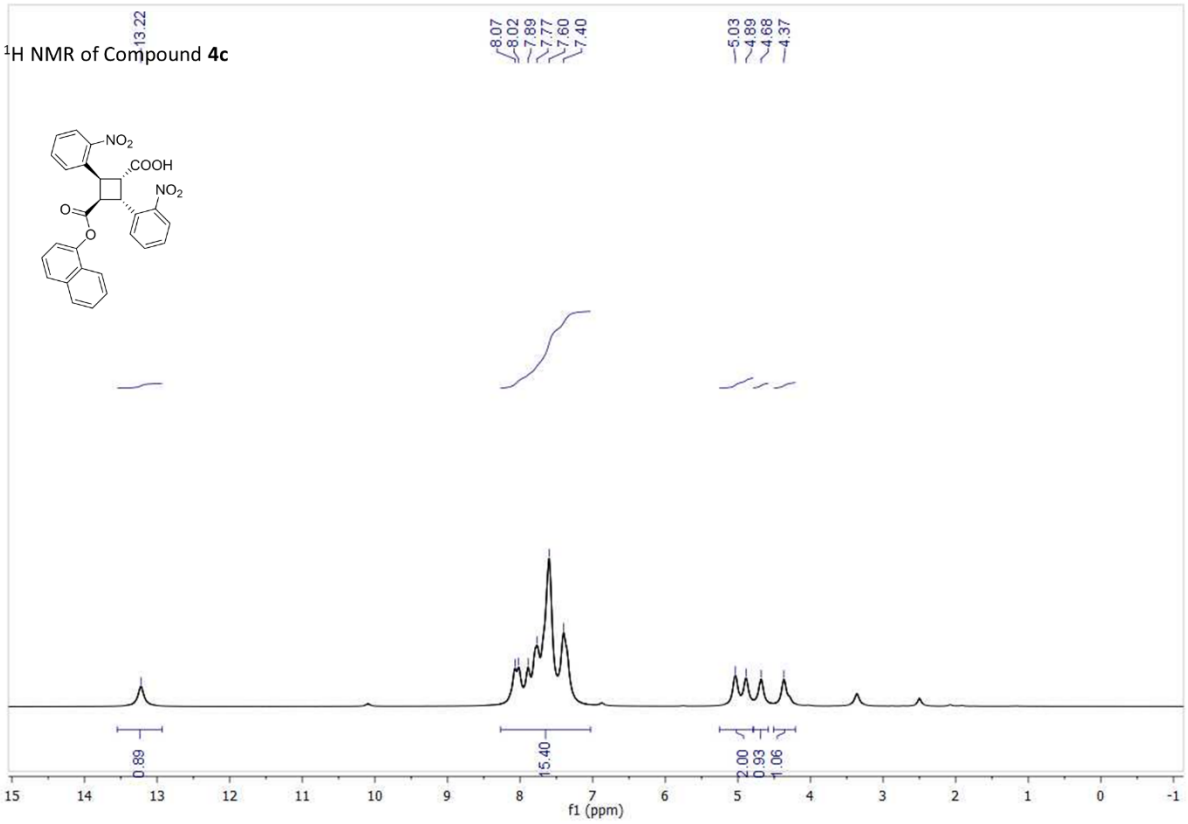
^{1}H NMR of Compound **4b**



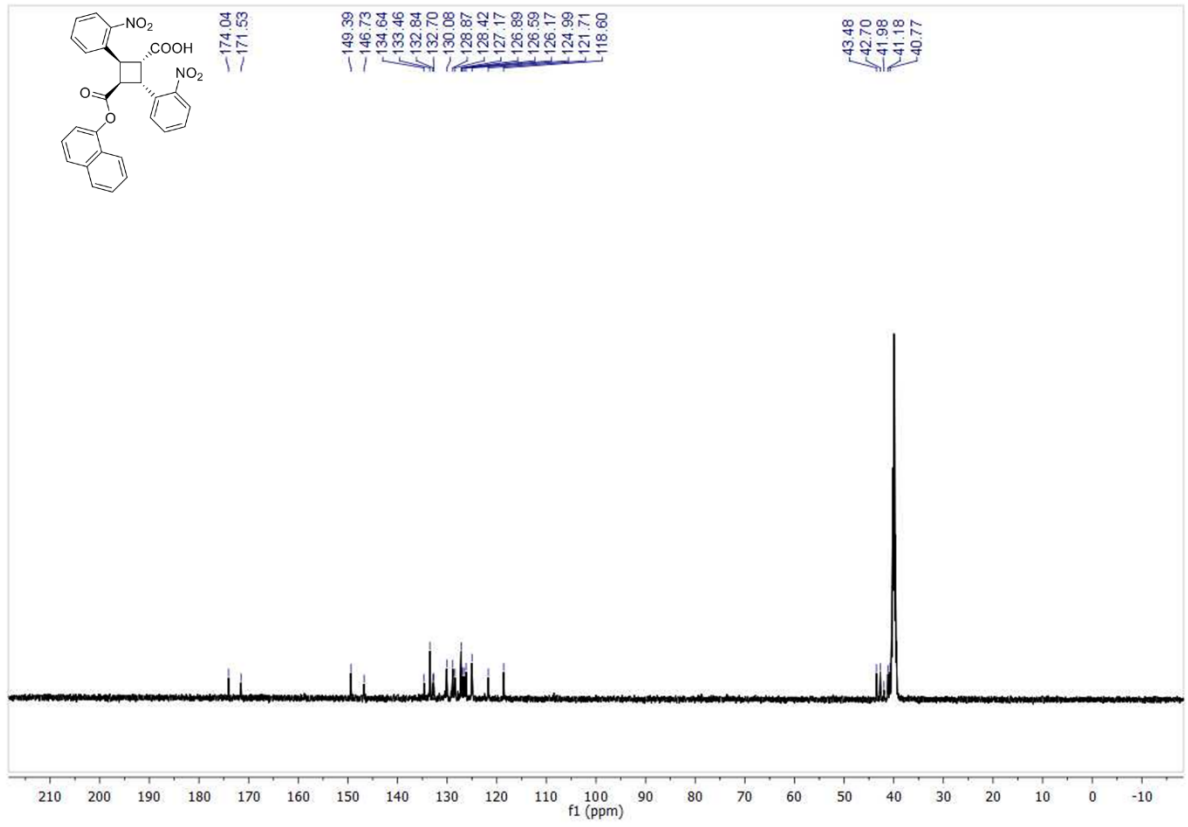
^{13}C NMR of Compound **4b**



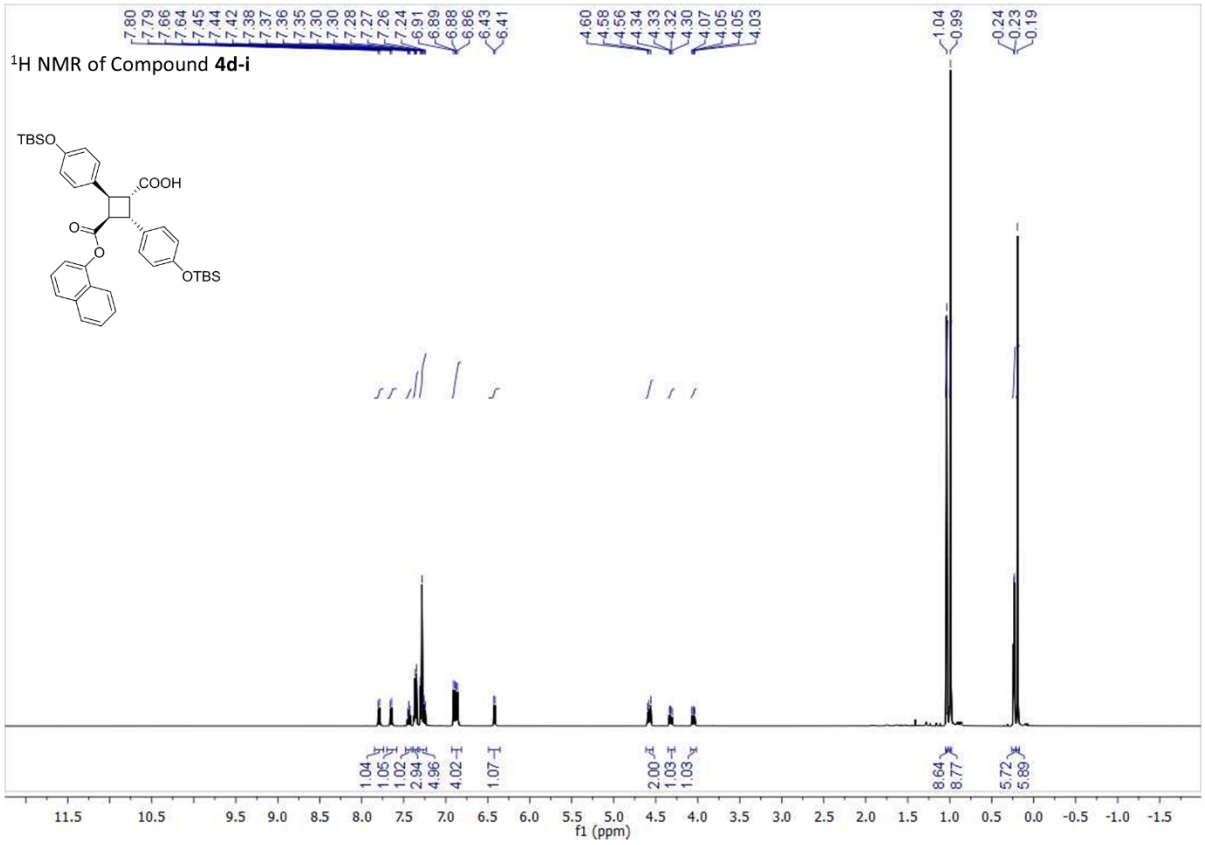
^{1}H NMR of Compound **4c**



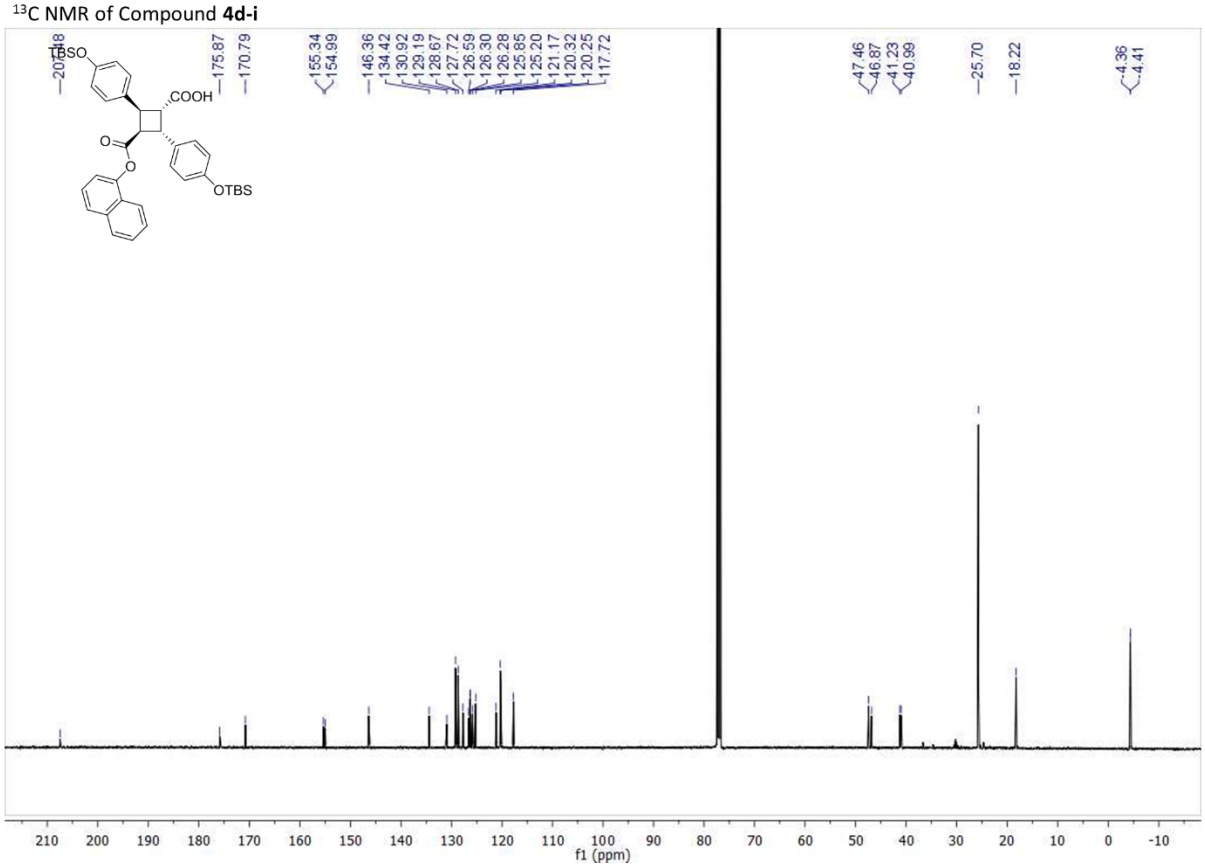
^{13}C NMR of Compound **4c**



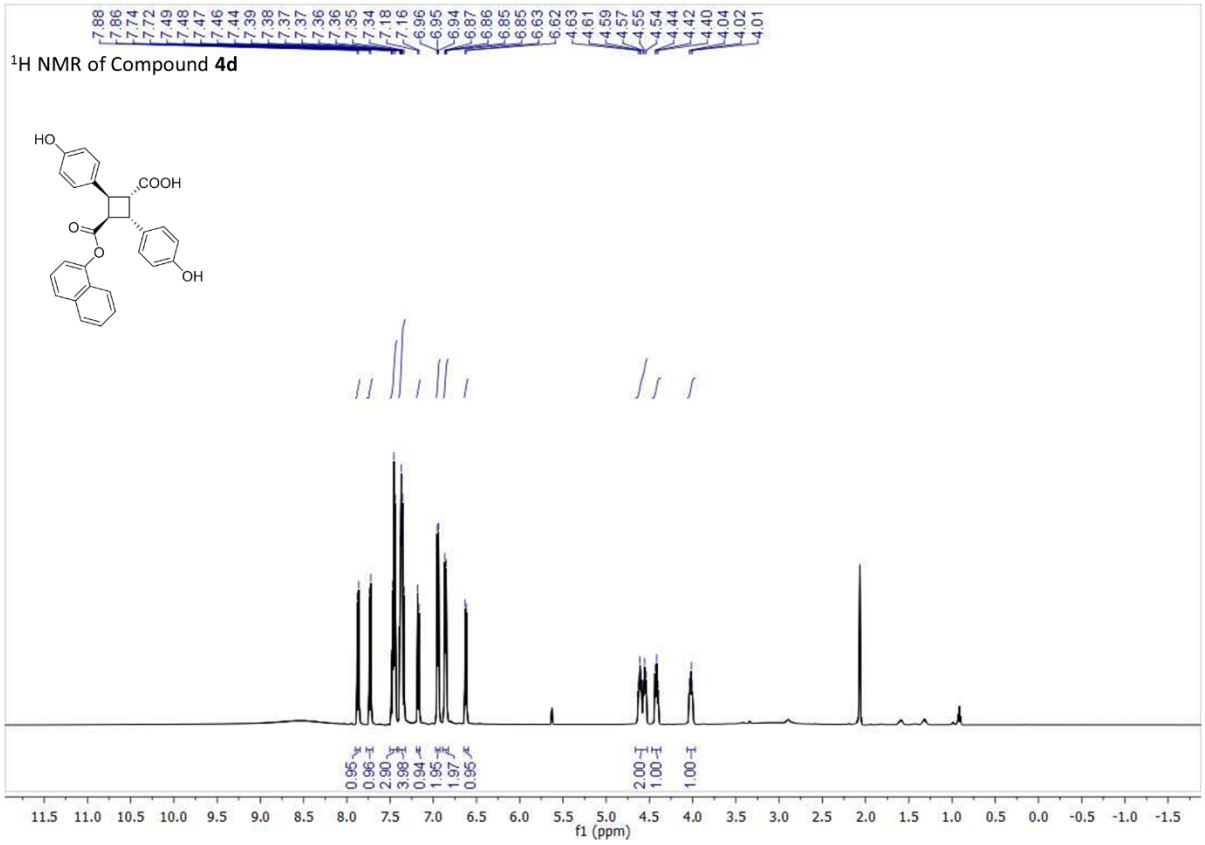
^{1}H NMR of Compound **4d-i**



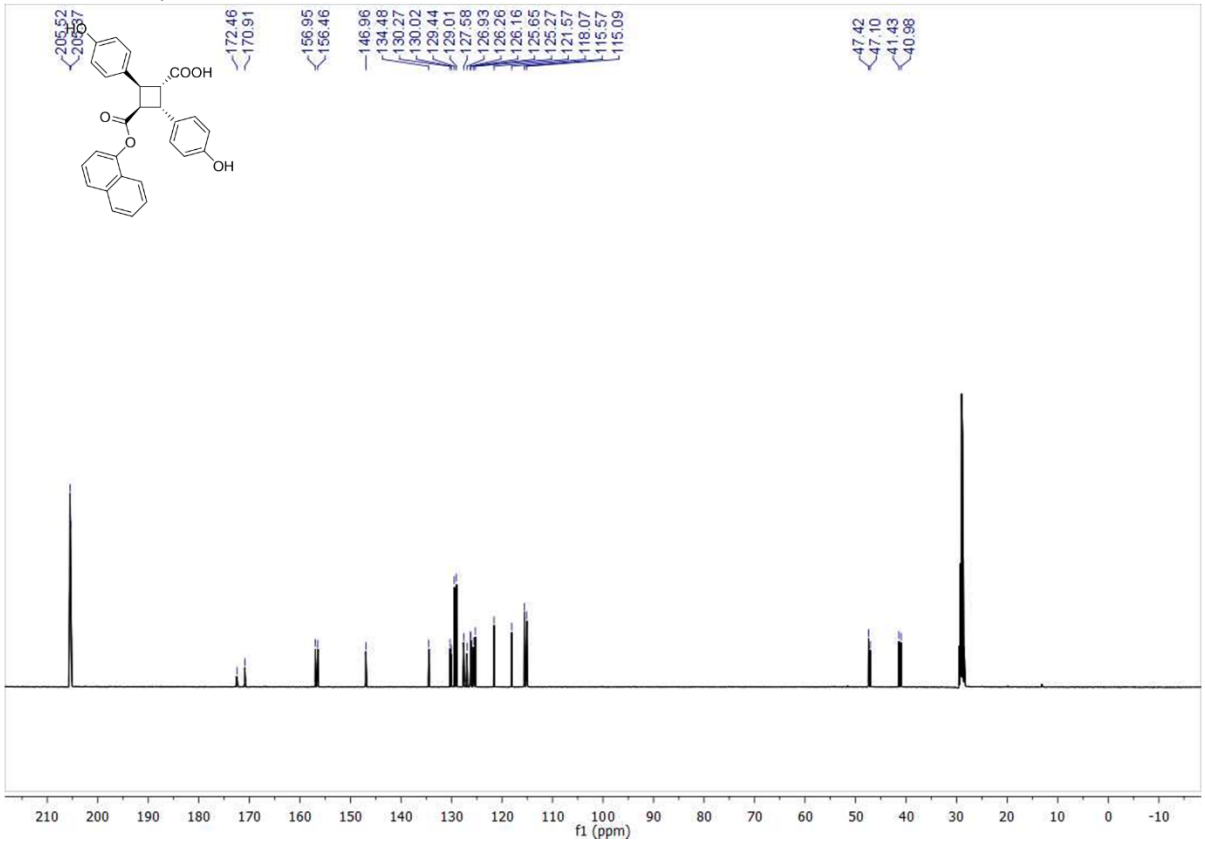
^{13}C NMR of Compound **4d-i**



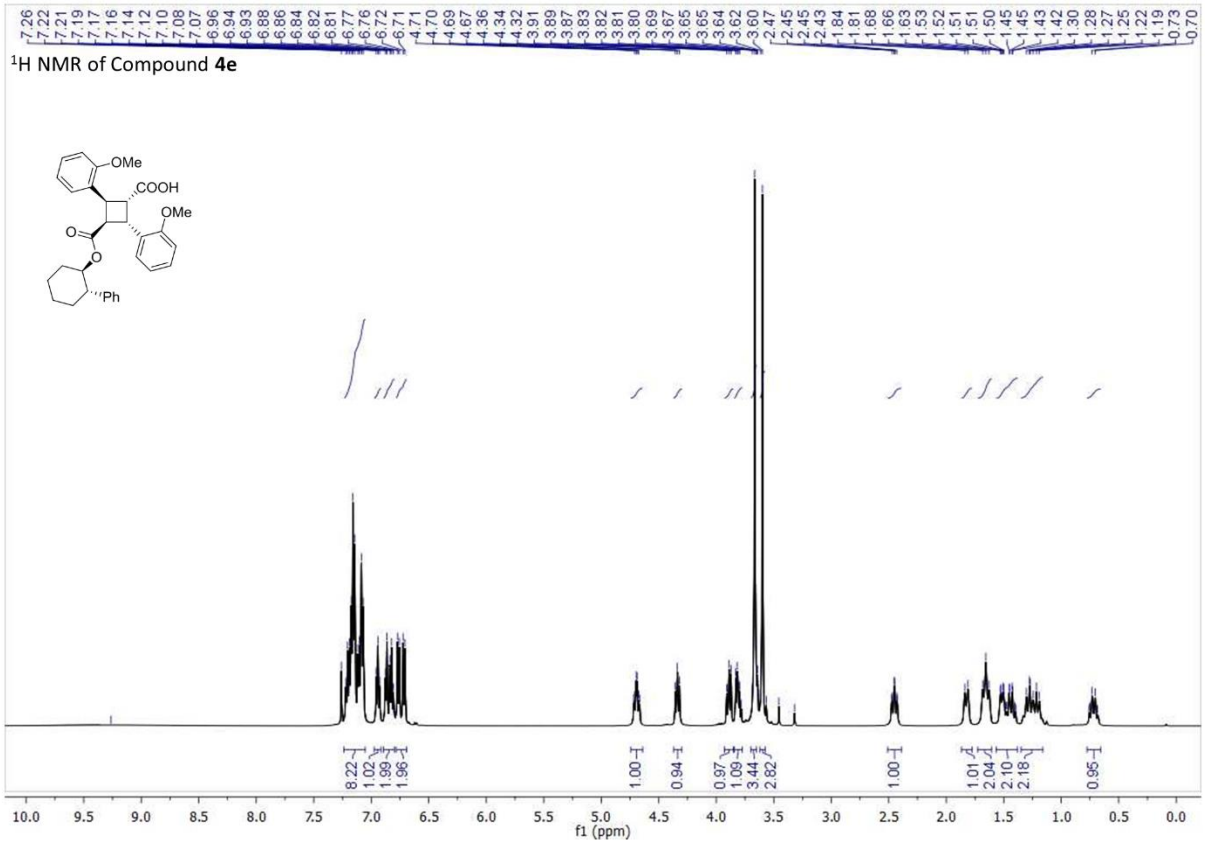
^{1}H NMR of Compound **4d**



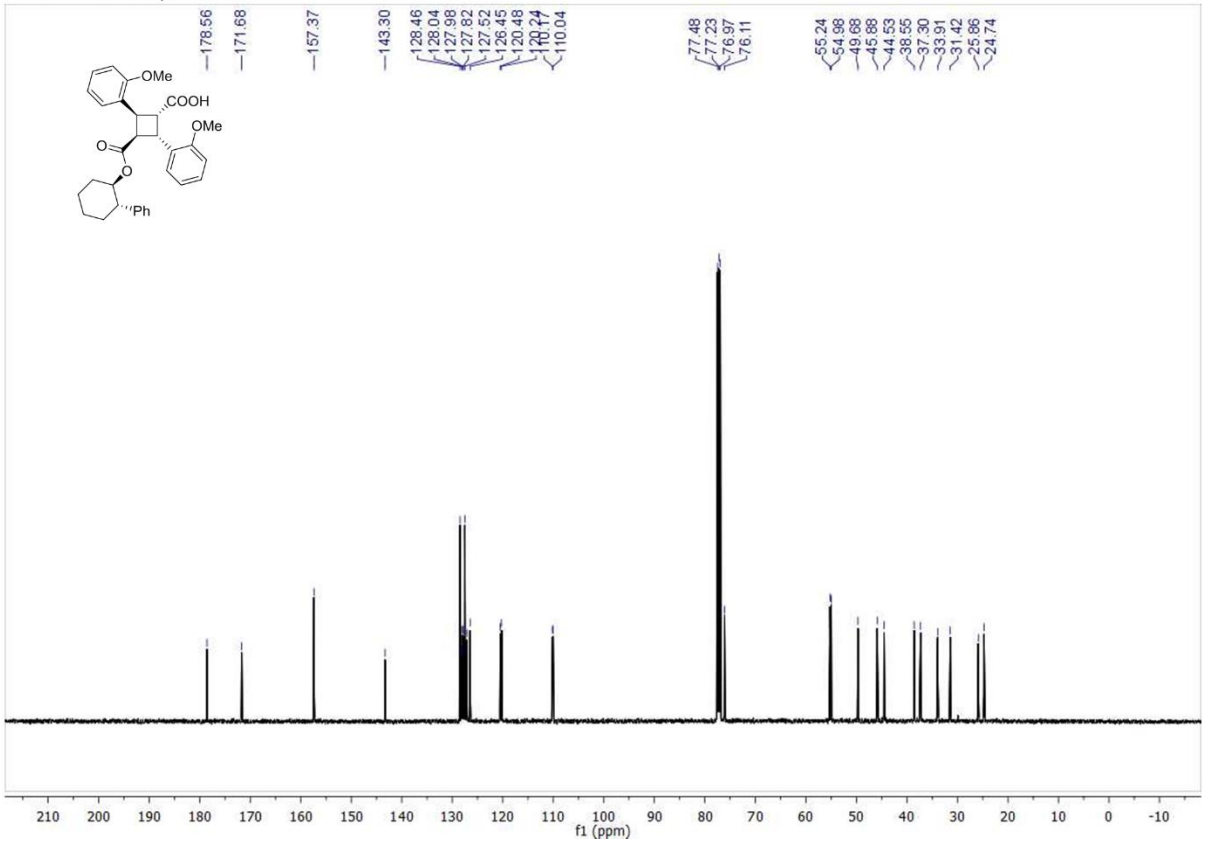
^{13}C NMR of Compound **4d**



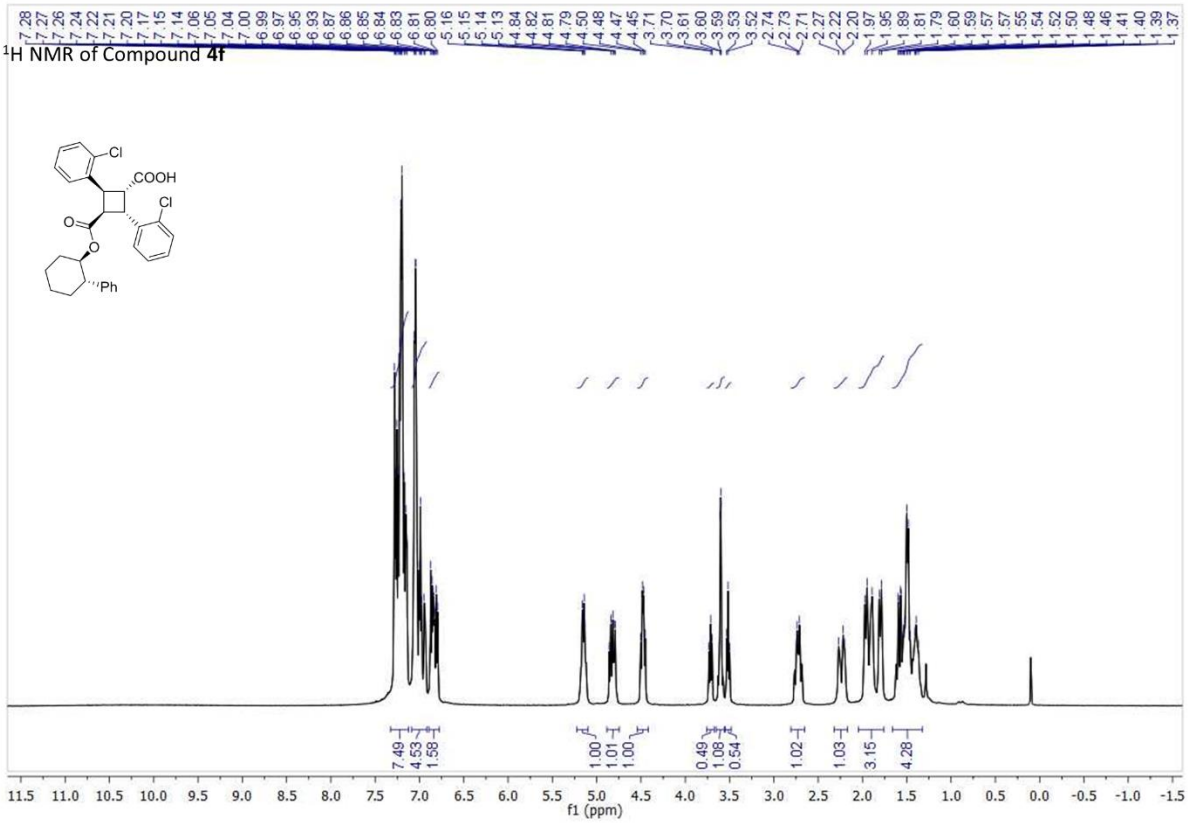
^{1}H NMR of Compound **4e**



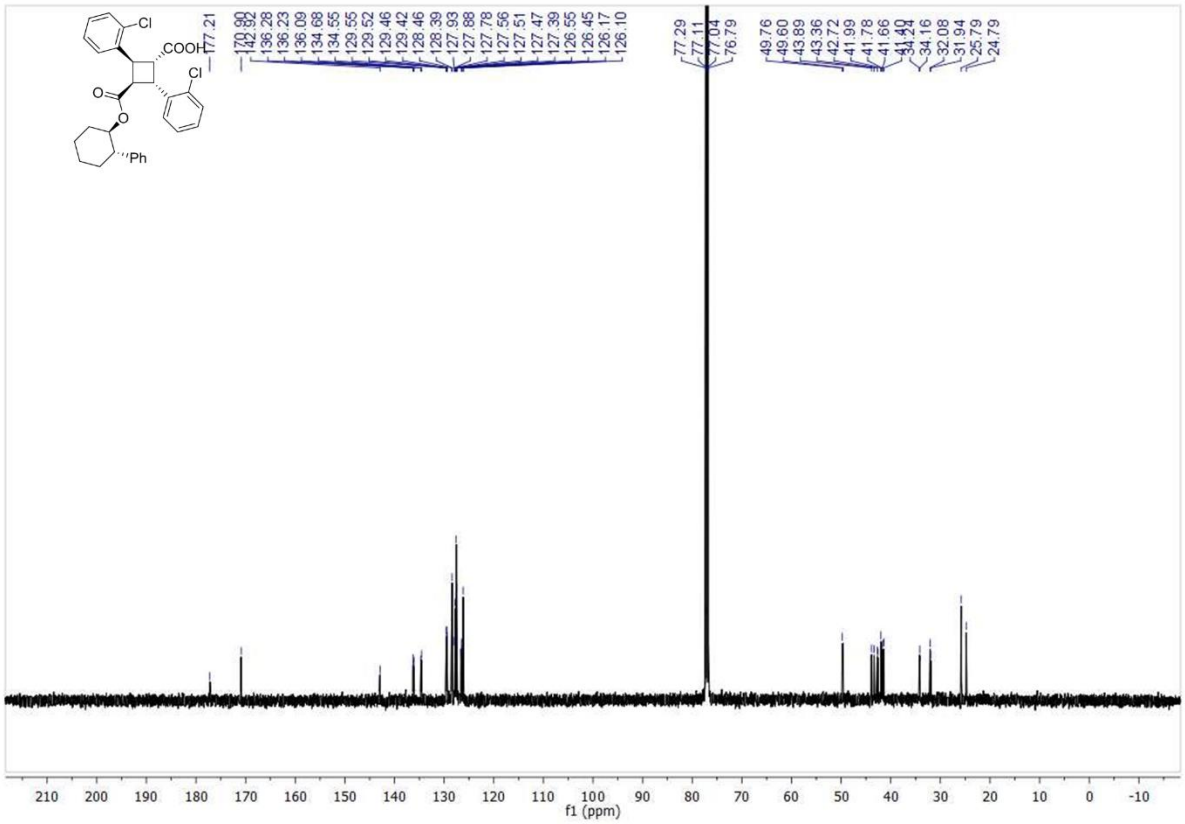
^{13}C NMR of Compound **4e**



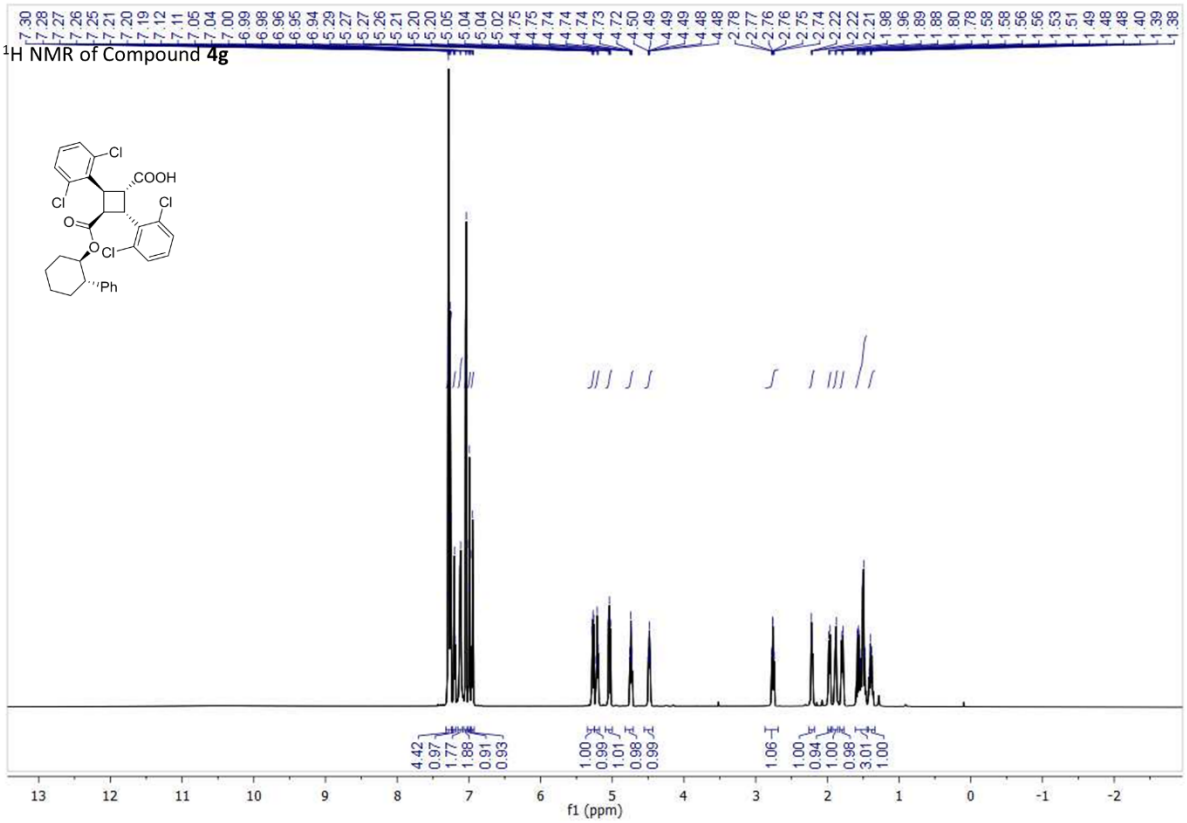
^{1}H NMR of Compound **4f**



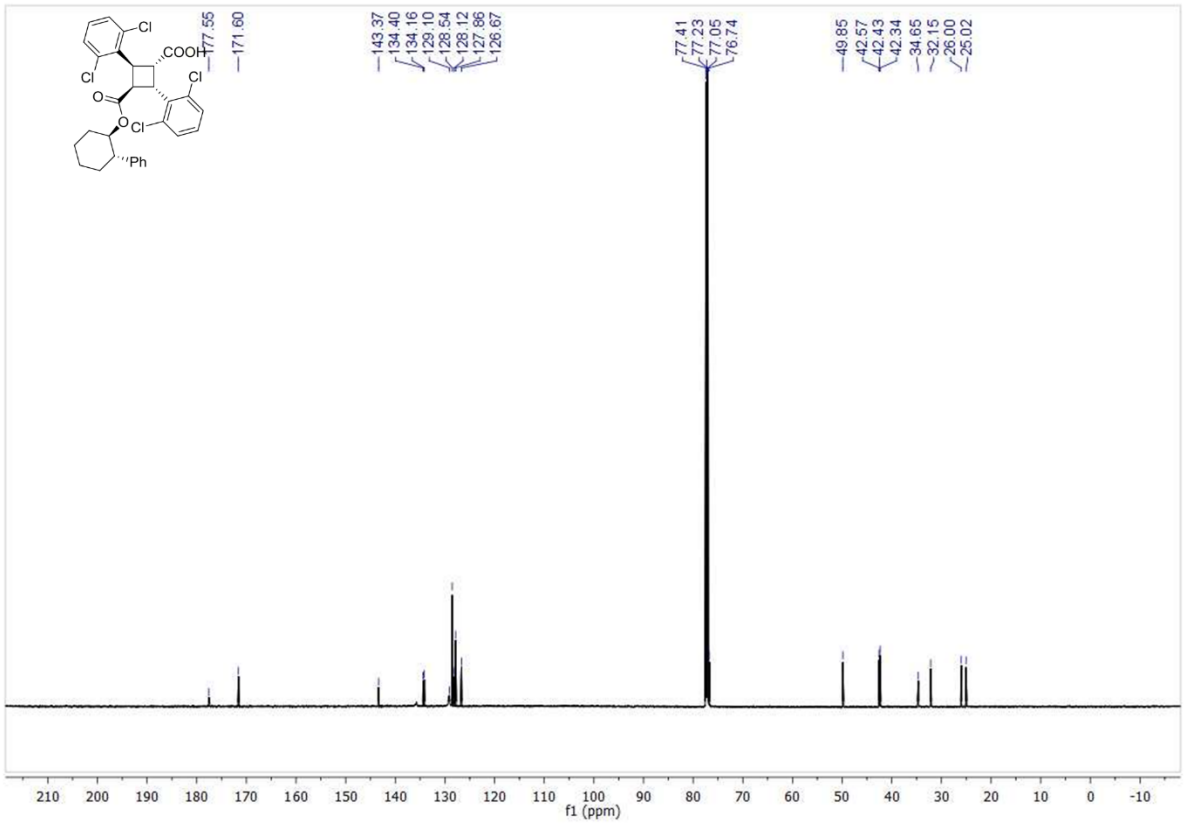
^{13}C NMR of Compound **4f**



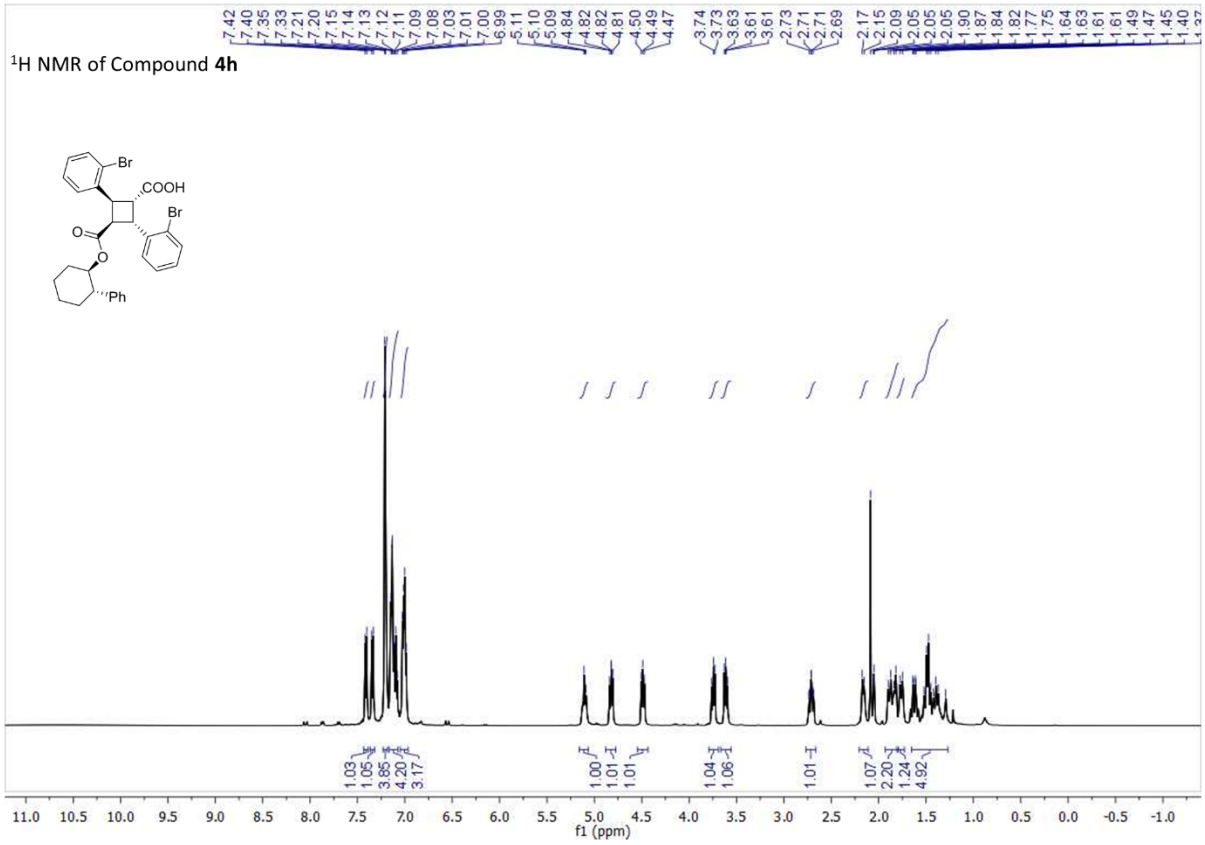
^{1}H NMR of Compound **4g**



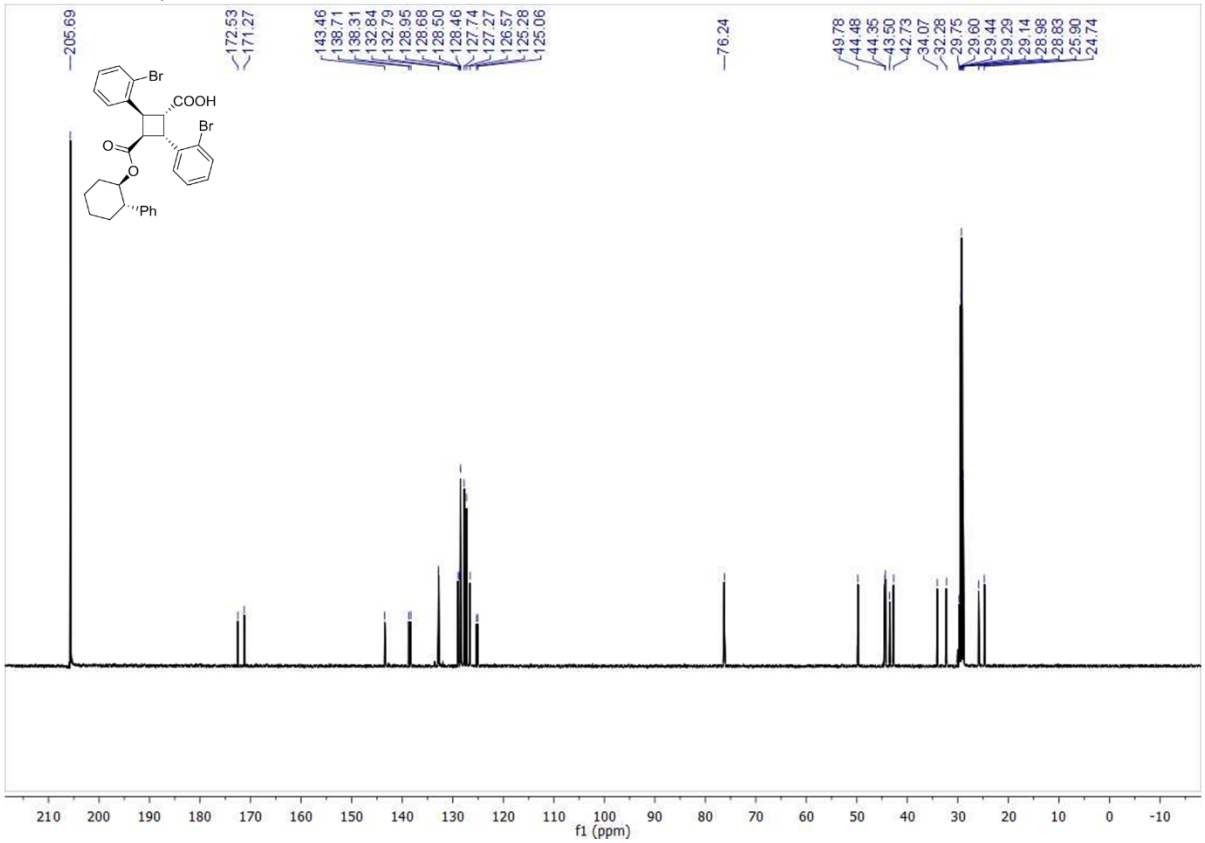
^{13}C NMR of Compound **4g**



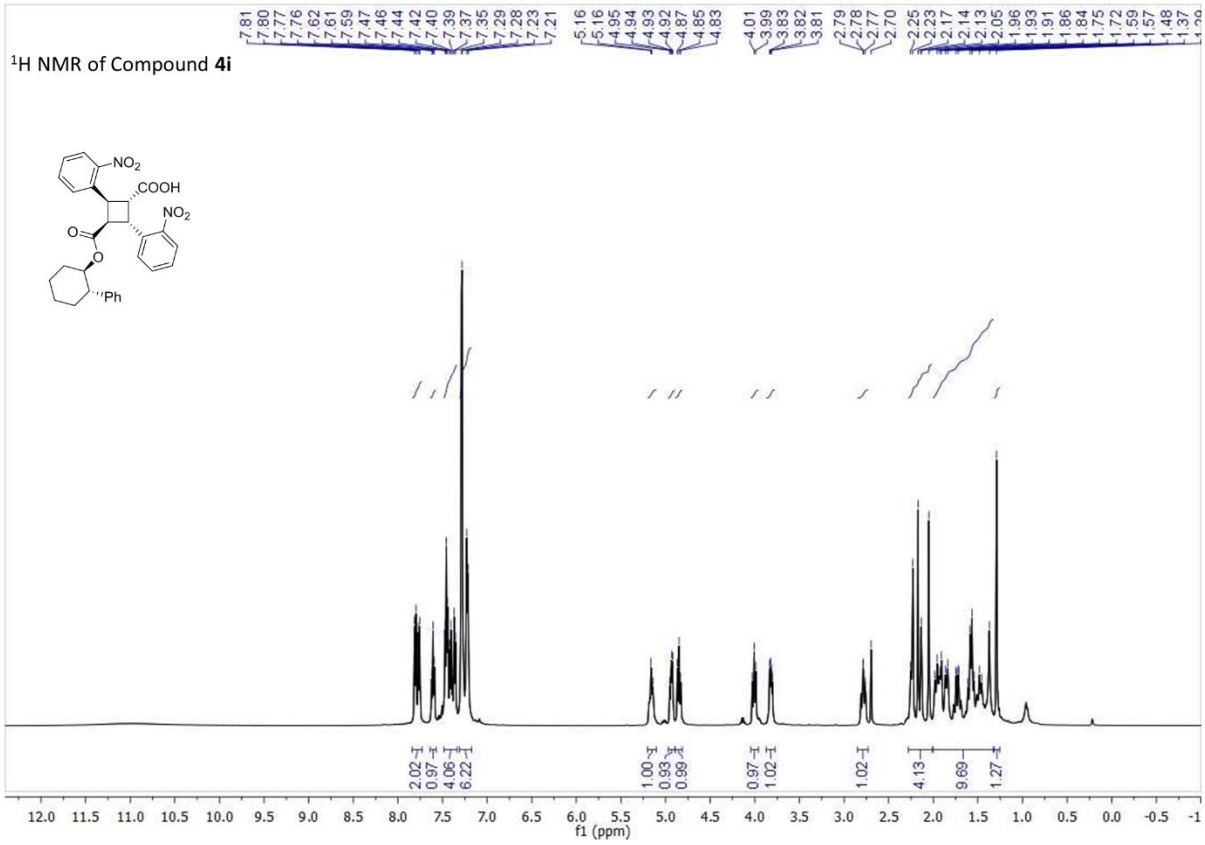
^{1}H NMR of Compound **4h**



^{13}C NMR of Compound **4h**



^{1}H NMR of Compound **4i**



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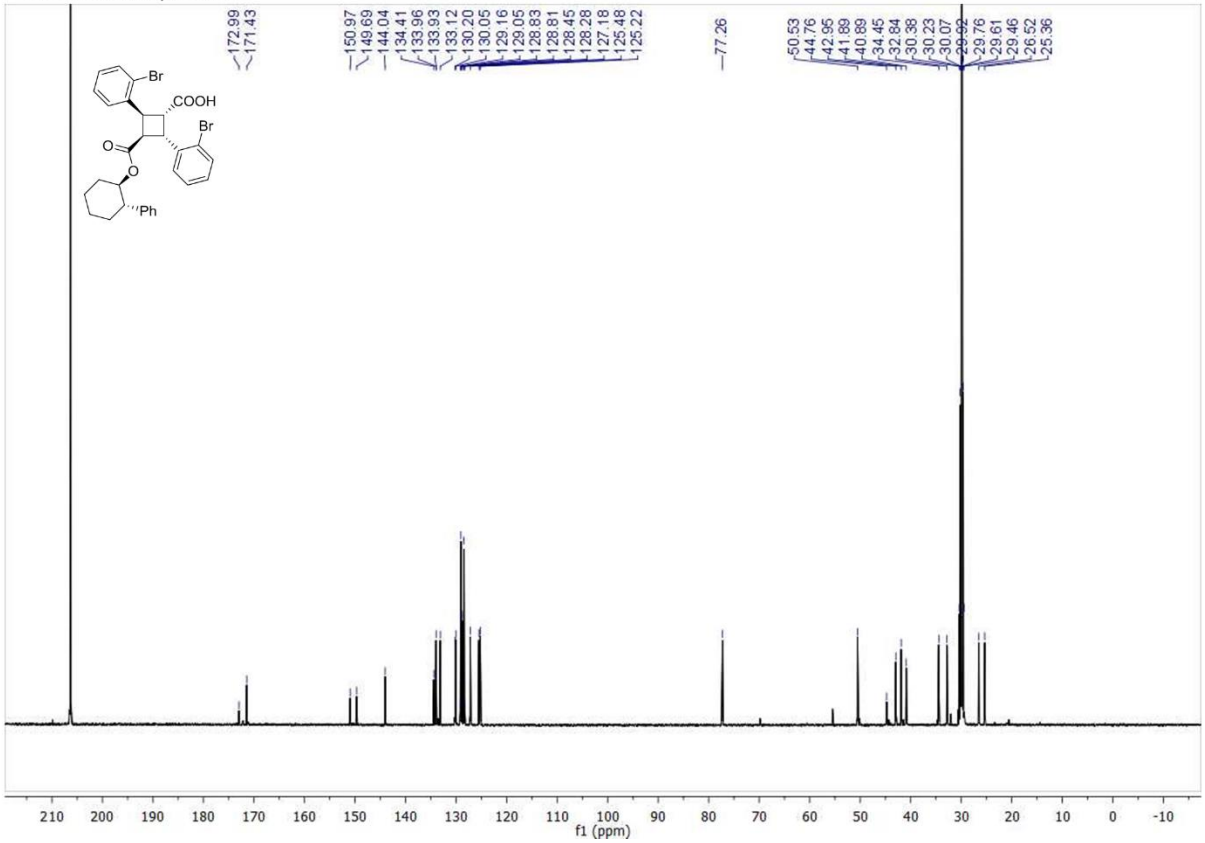

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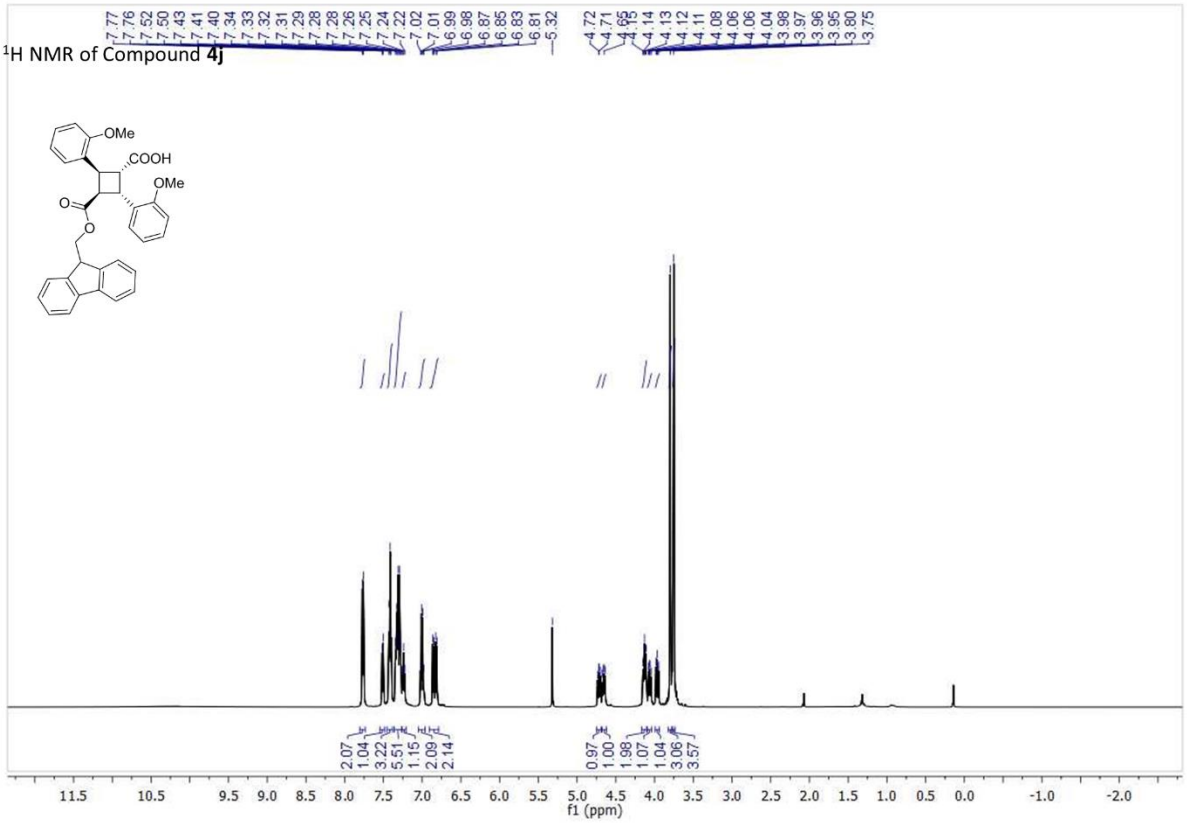
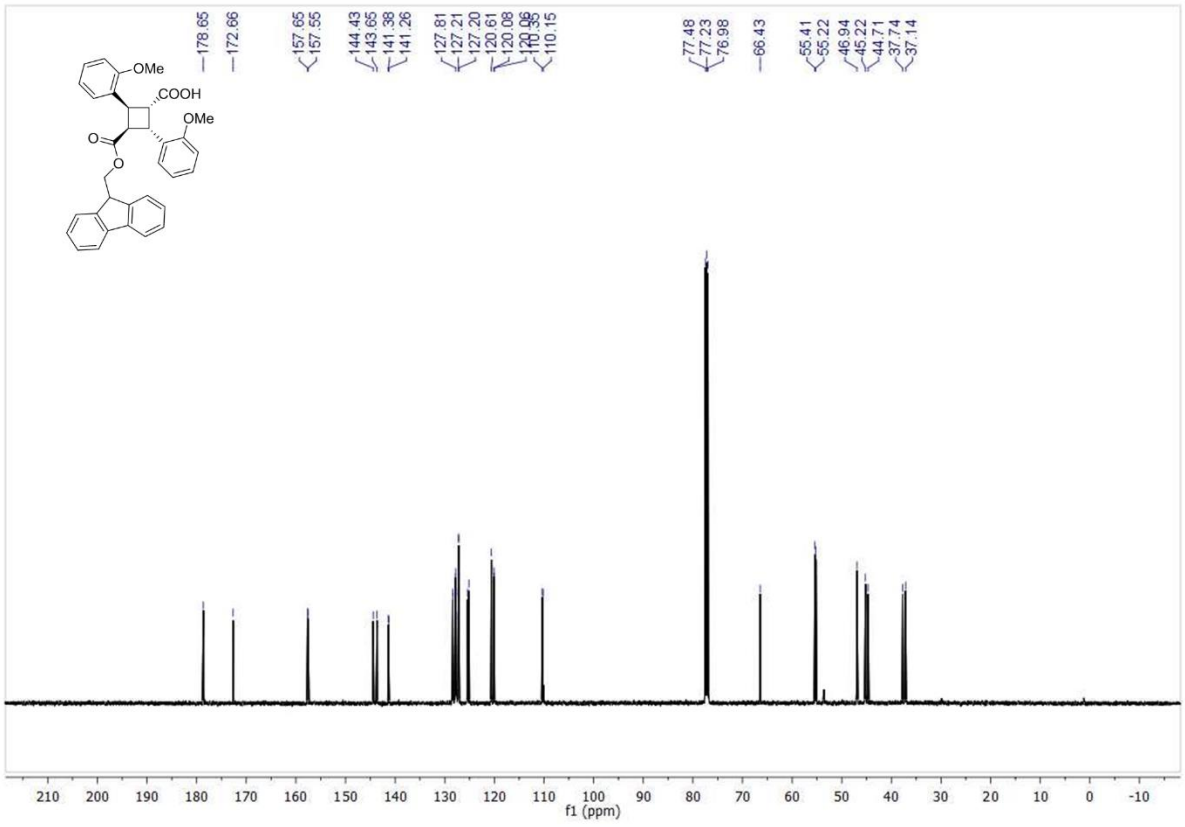


^{13}C NMR of Compound **4j**



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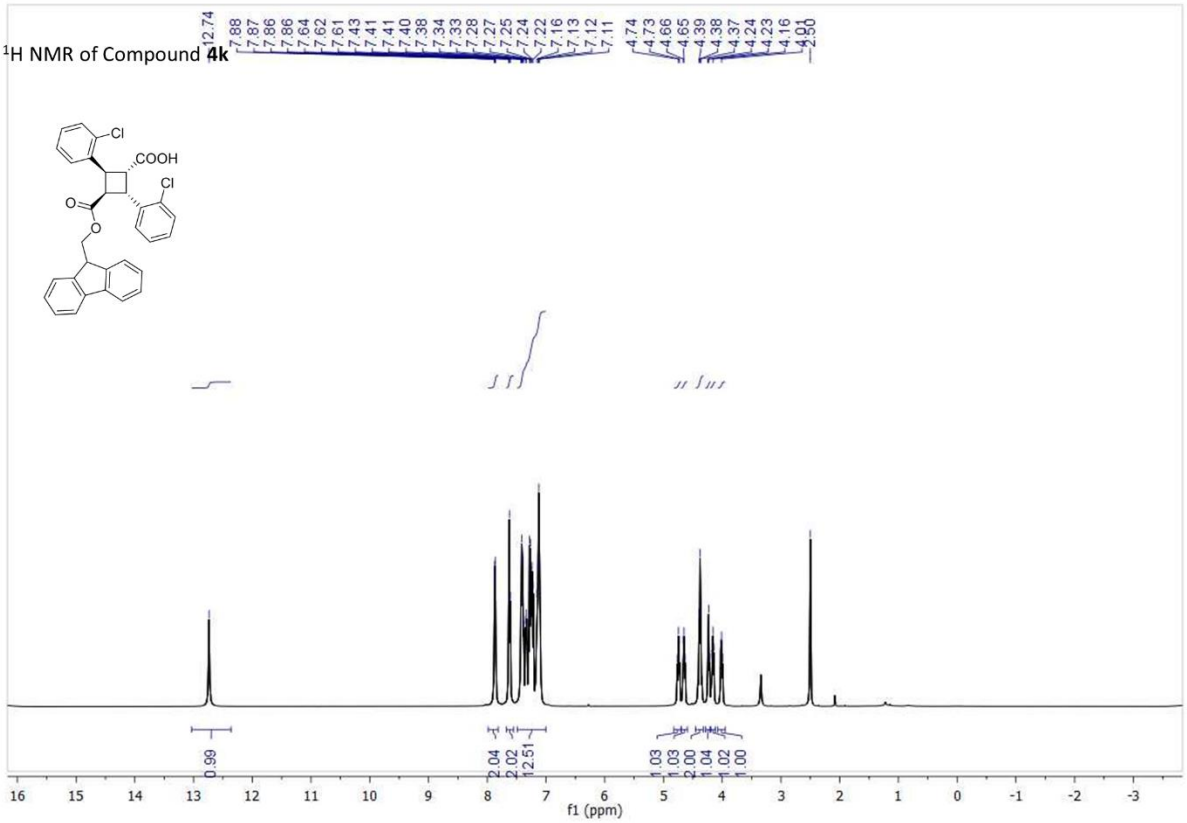

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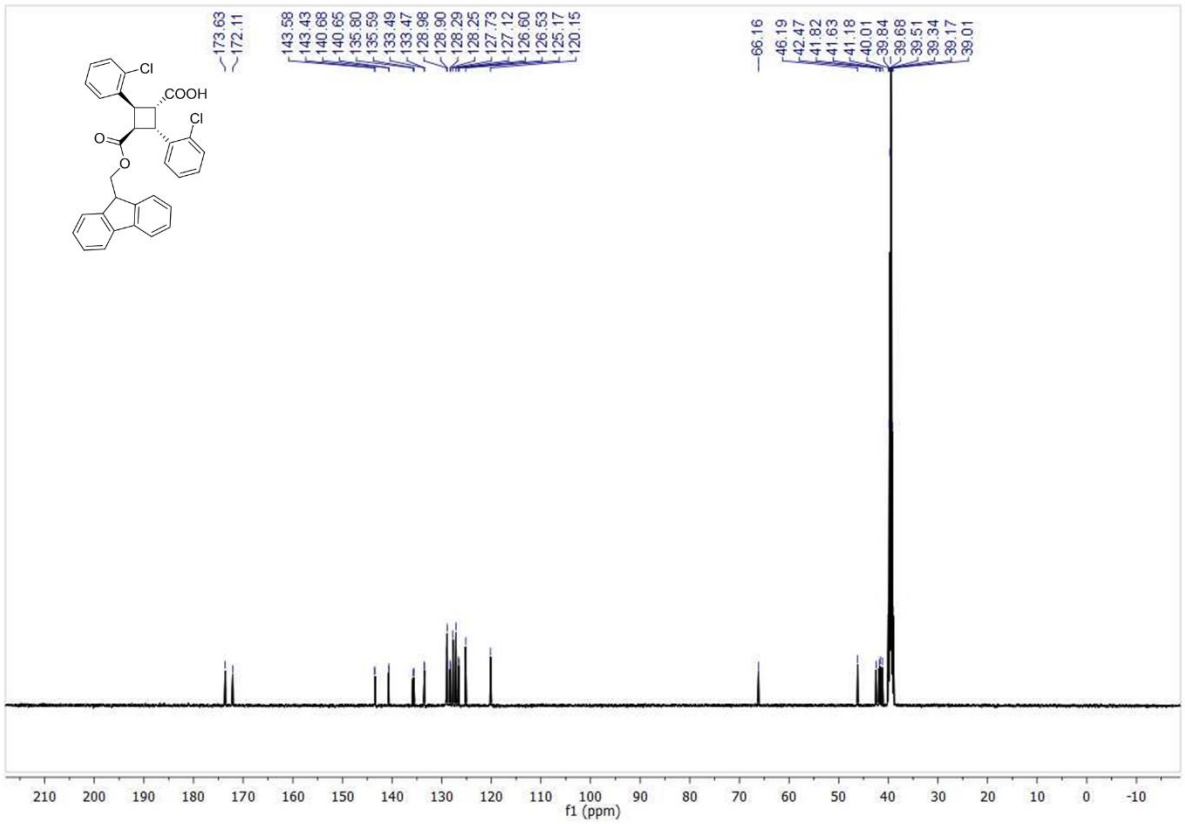

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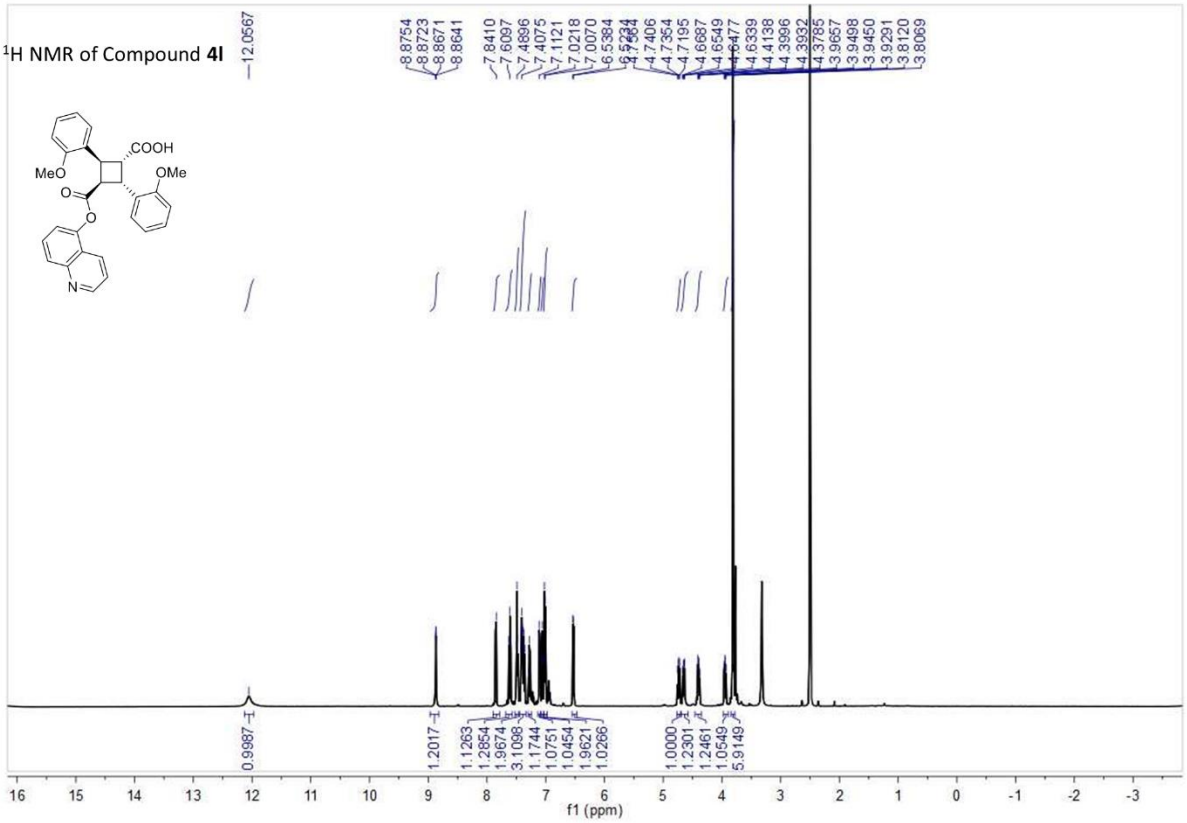
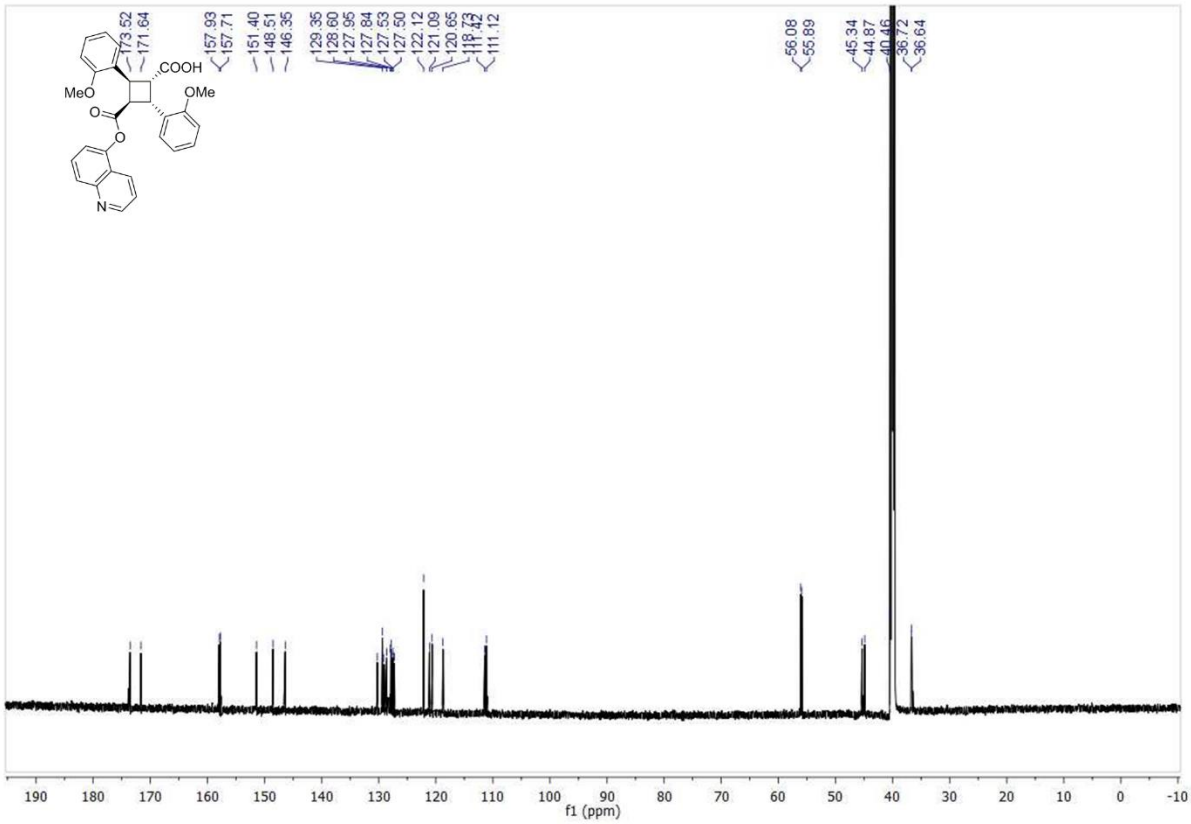
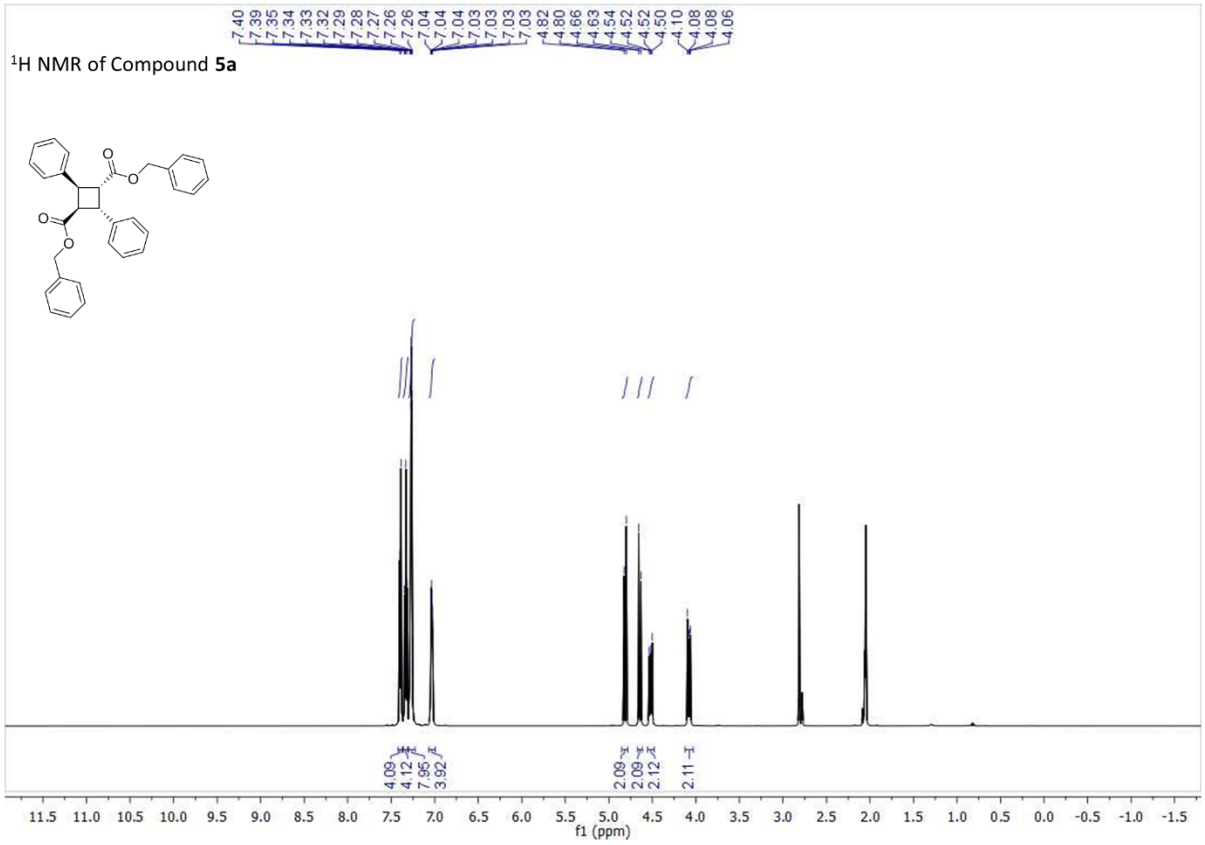


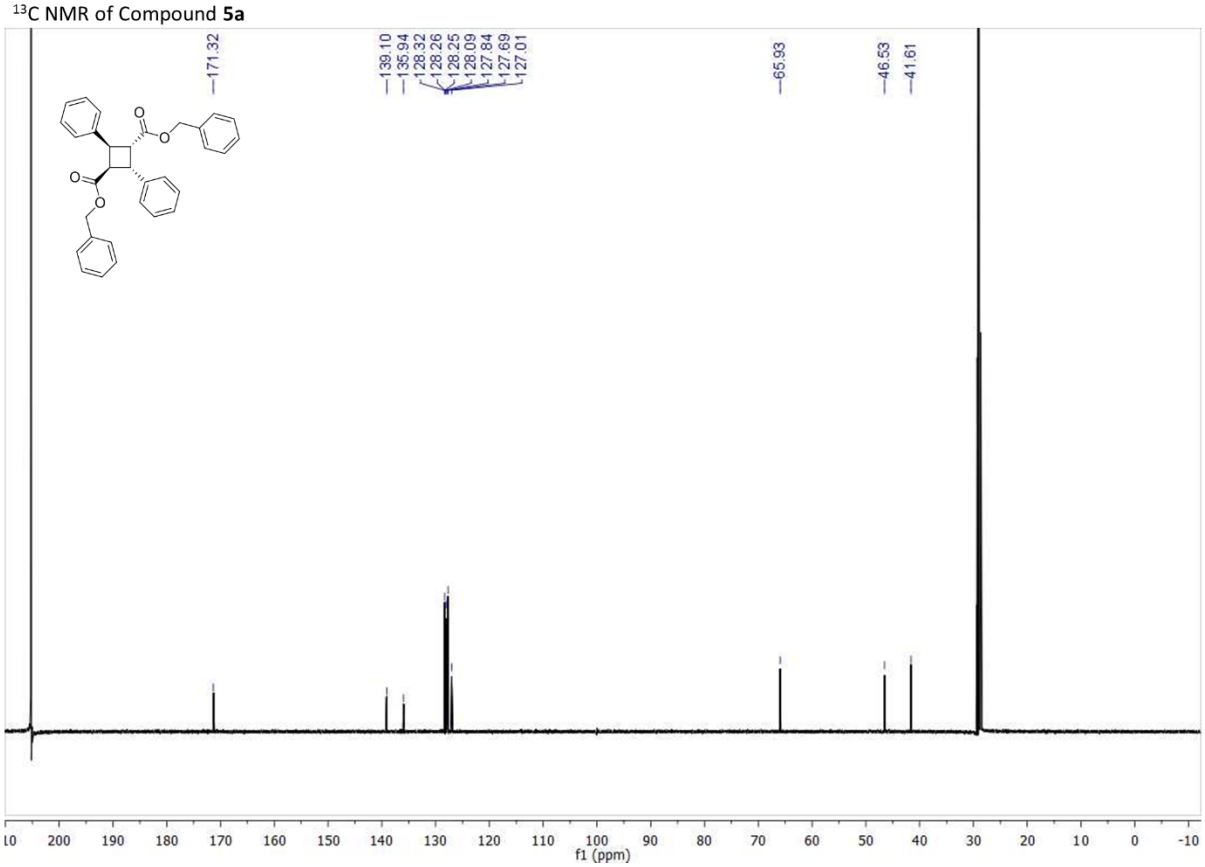
^{13}C NMR of Compound **4l**



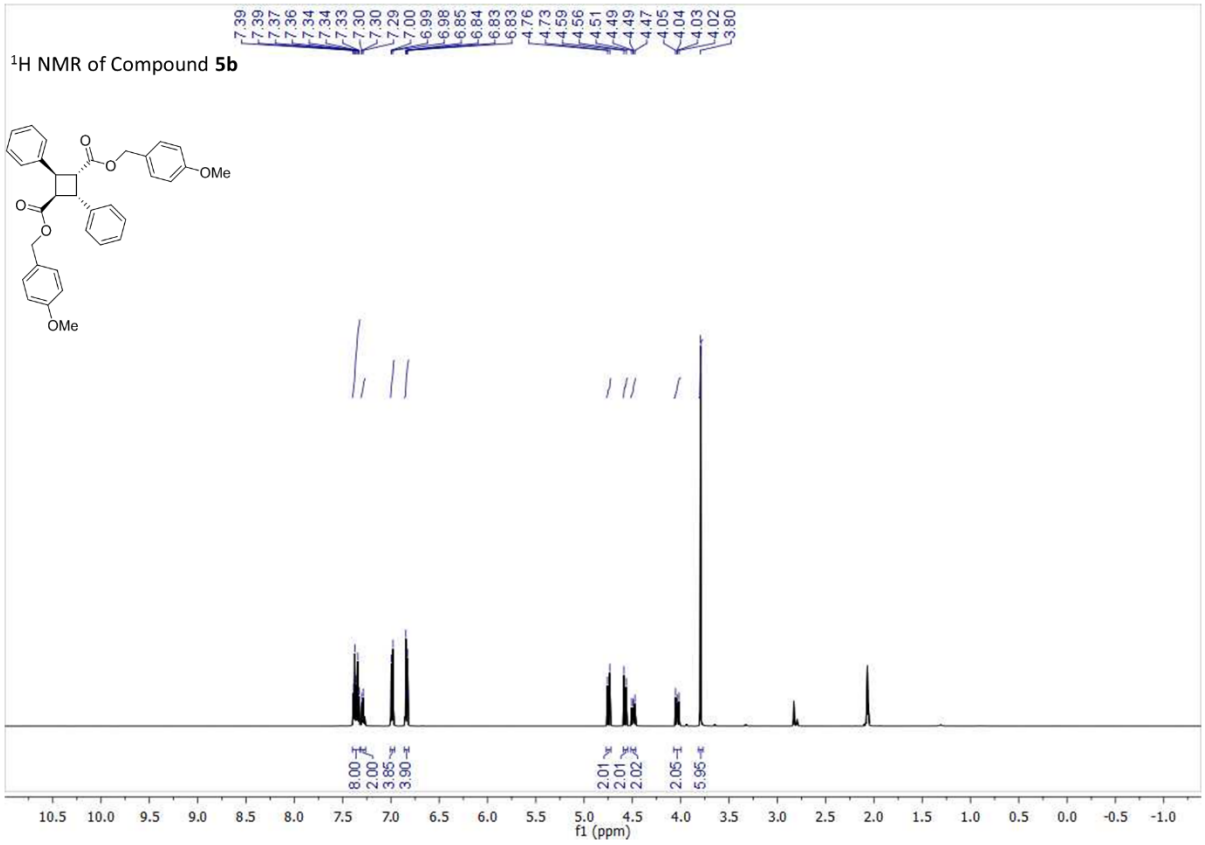
^{1}H NMR of Compound **5a**



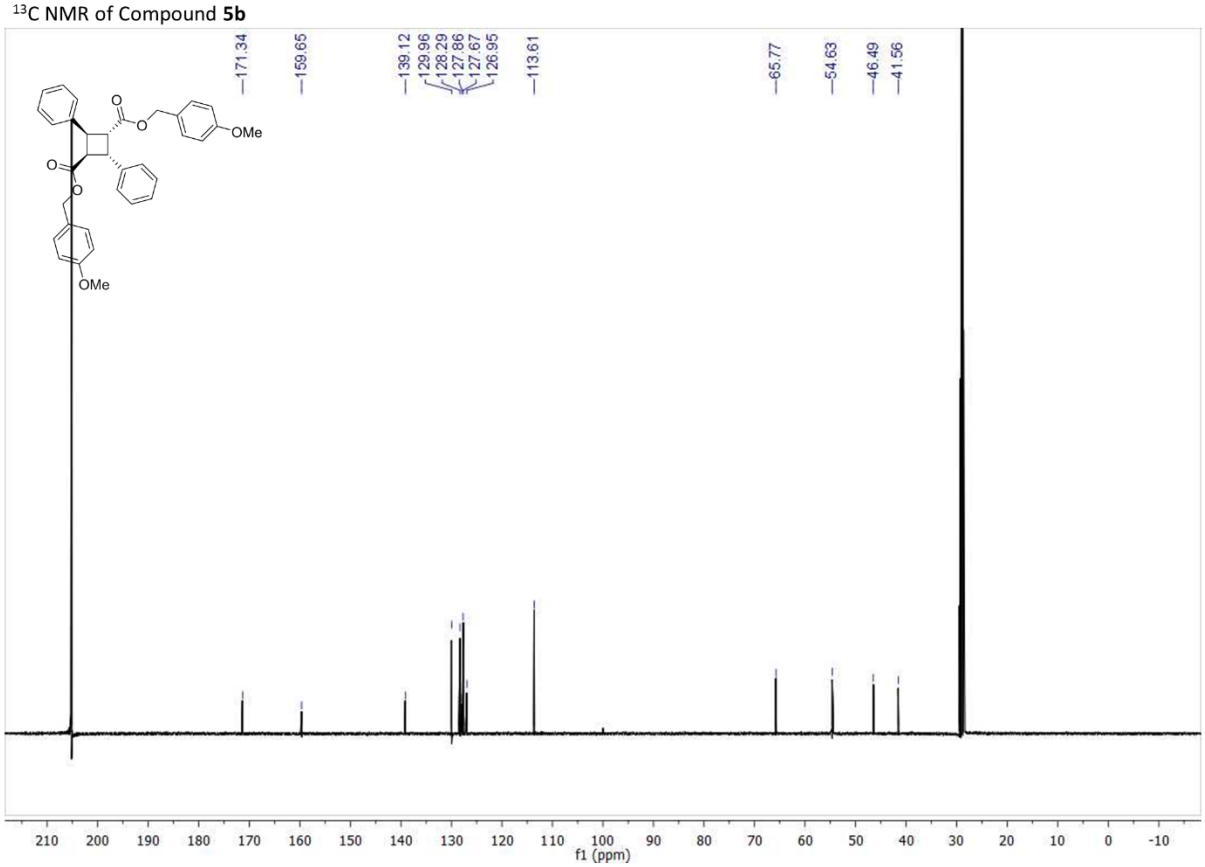
^{13}C NMR of Compound **5a**



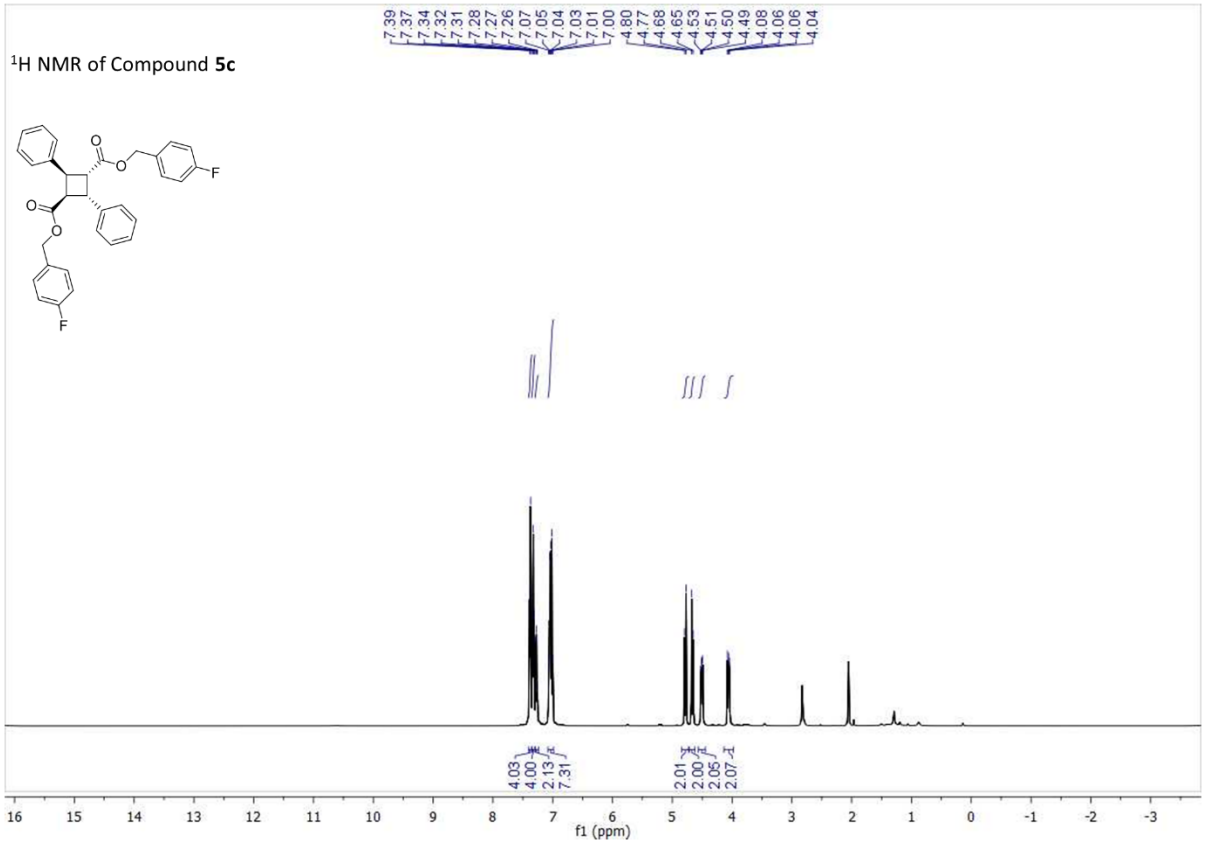
^{1}H NMR of Compound **5b**



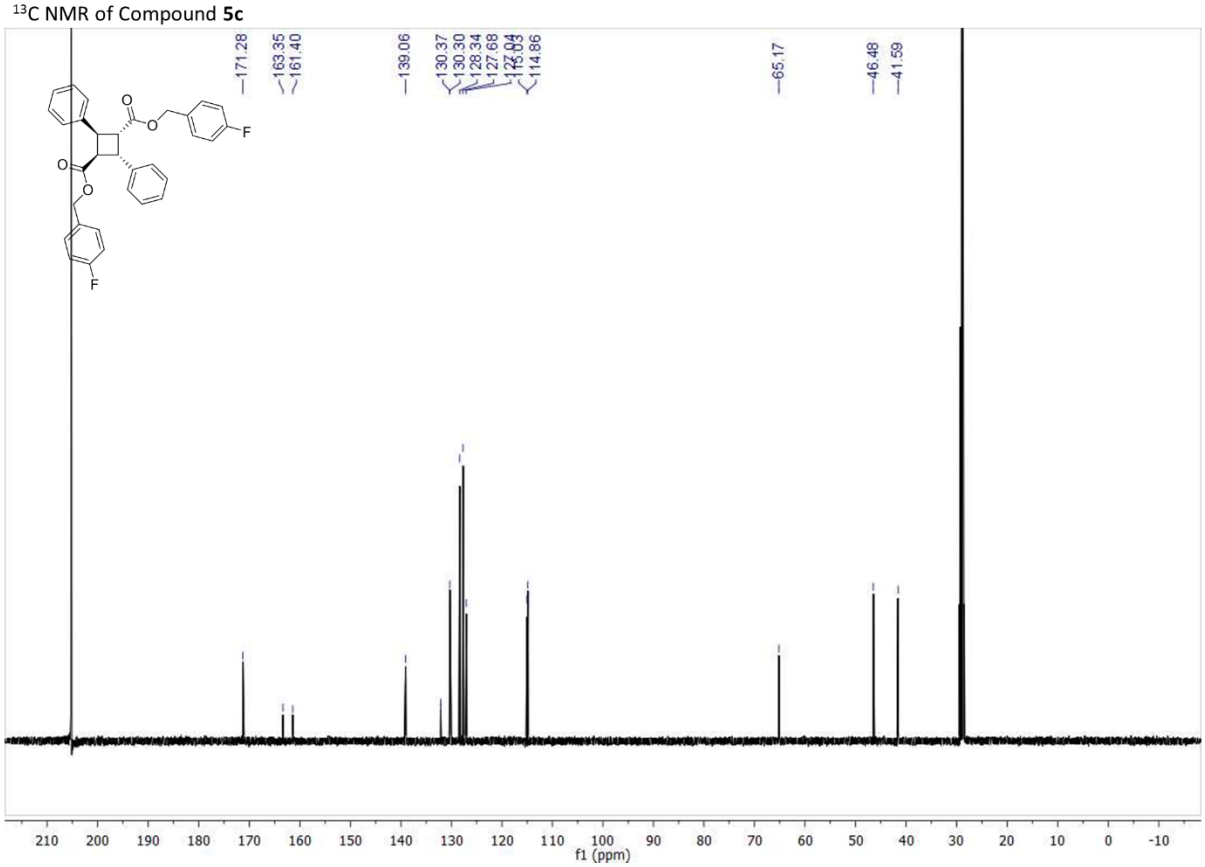
^{13}C NMR of Compound **5b**



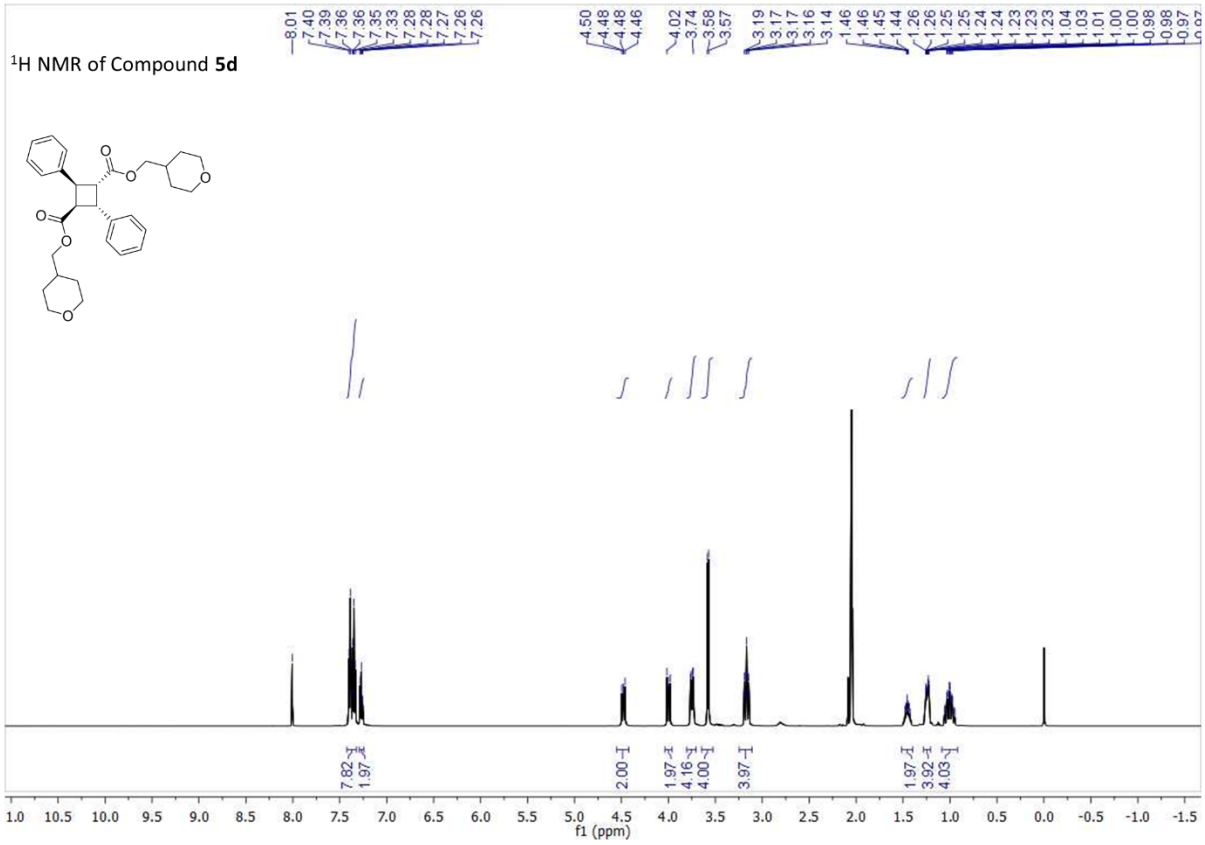
^{1}H NMR of Compound **5c**



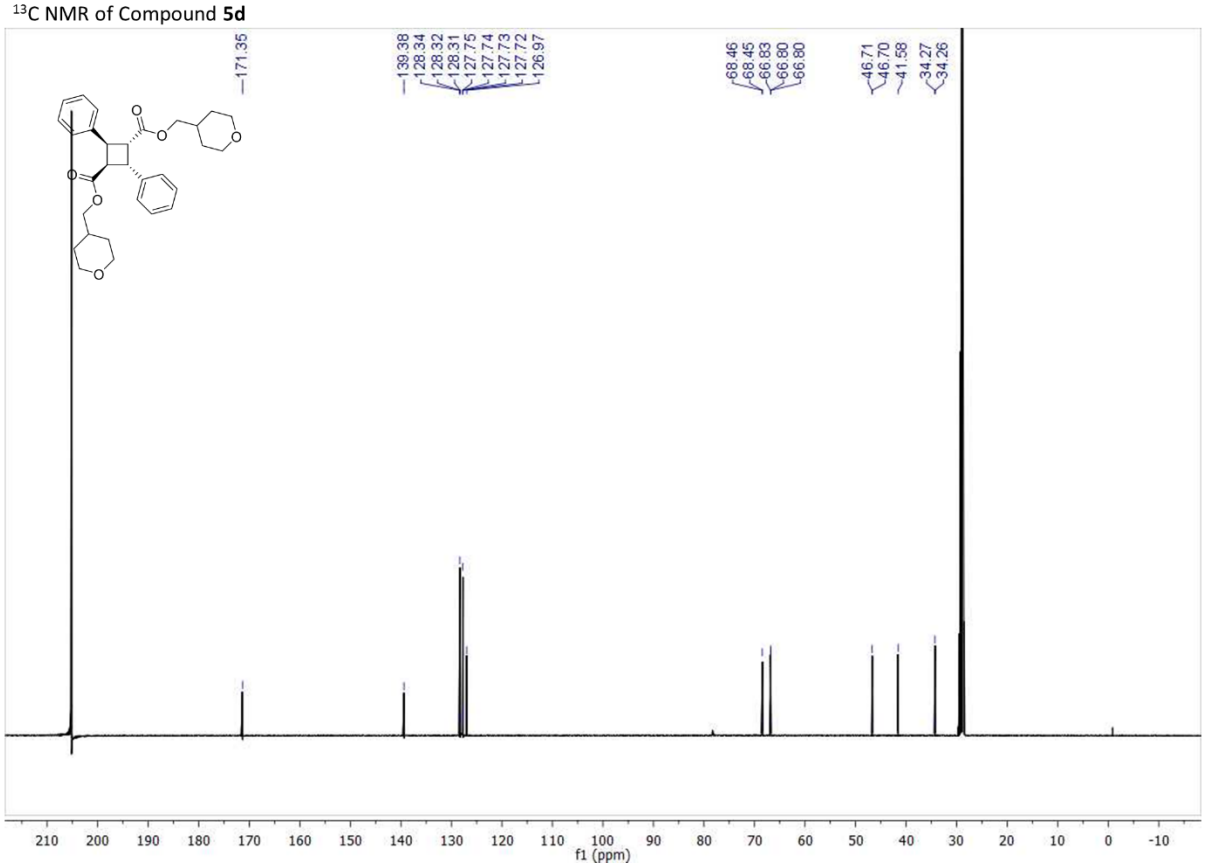
^{13}C NMR of Compound **5c**



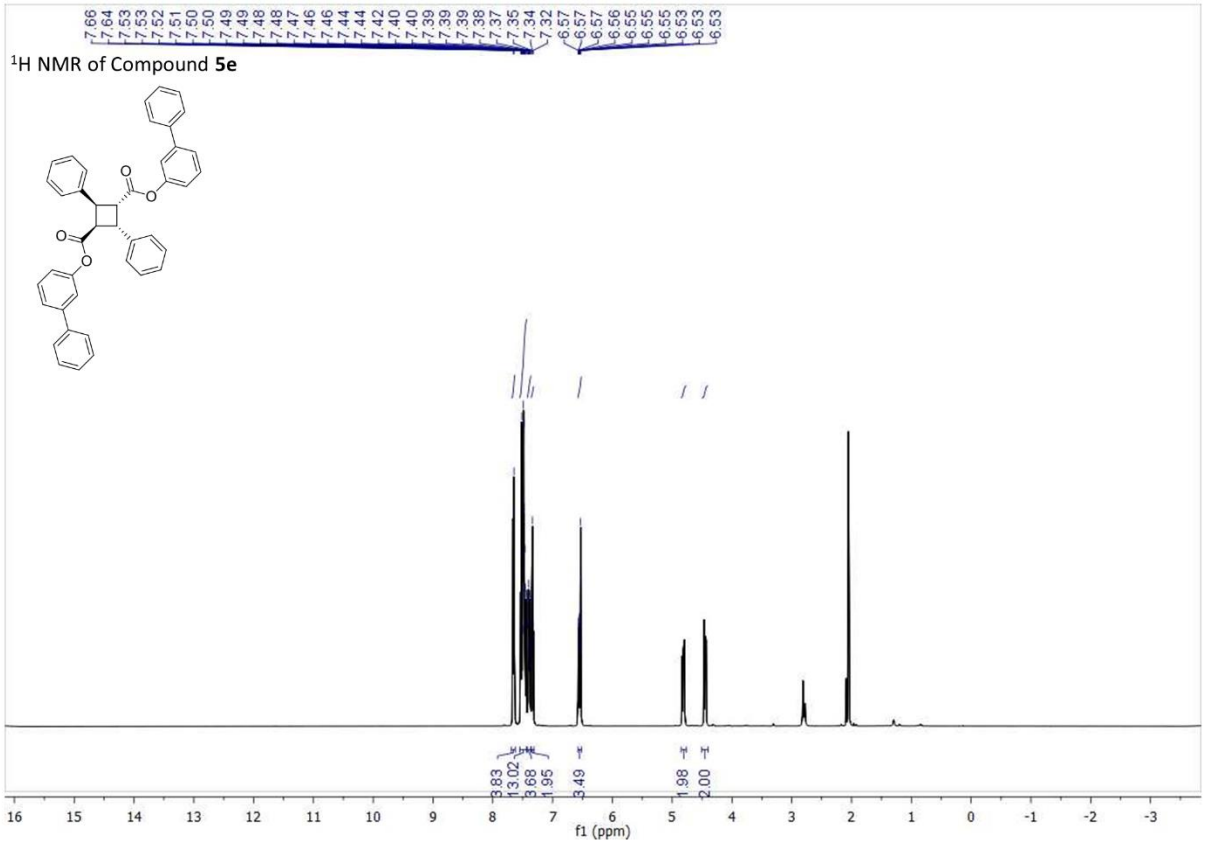
^{1}H NMR of Compound **5d**



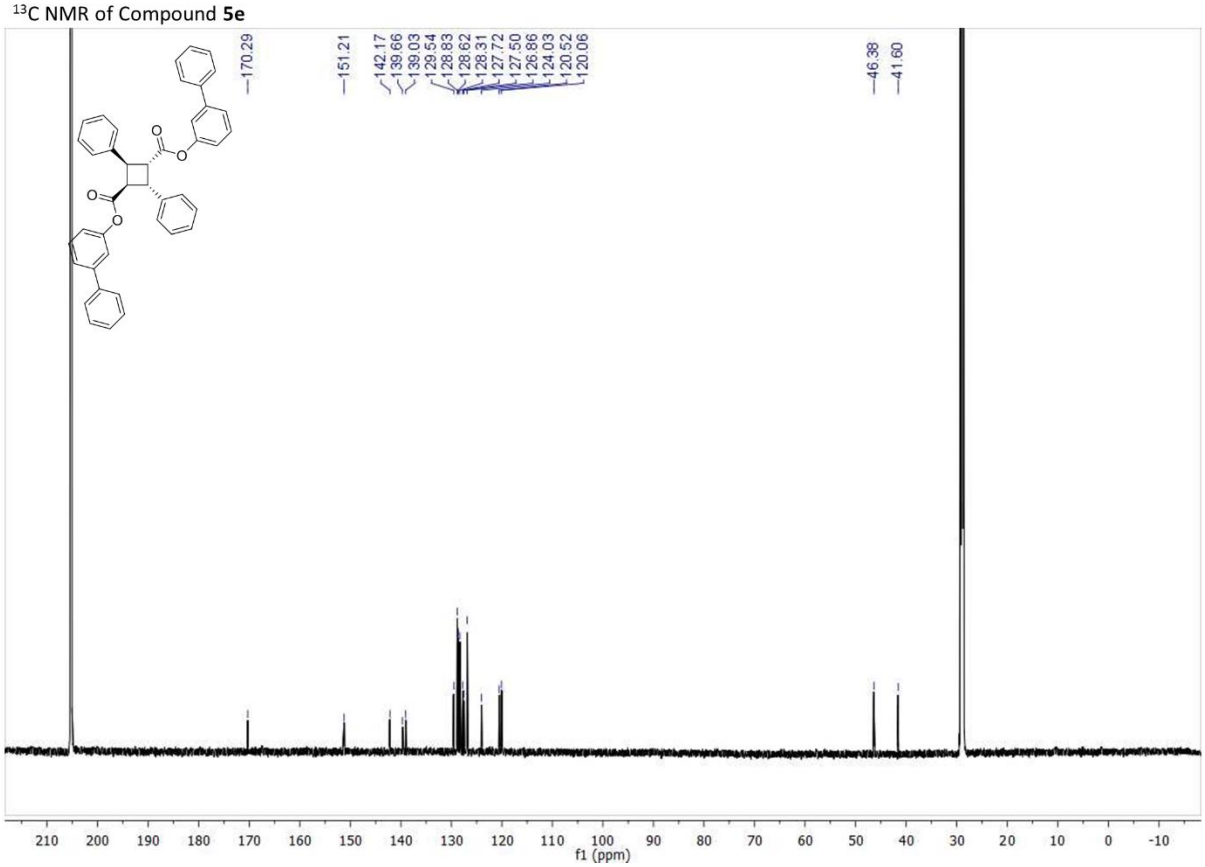
^{13}C NMR of Compound **5d**



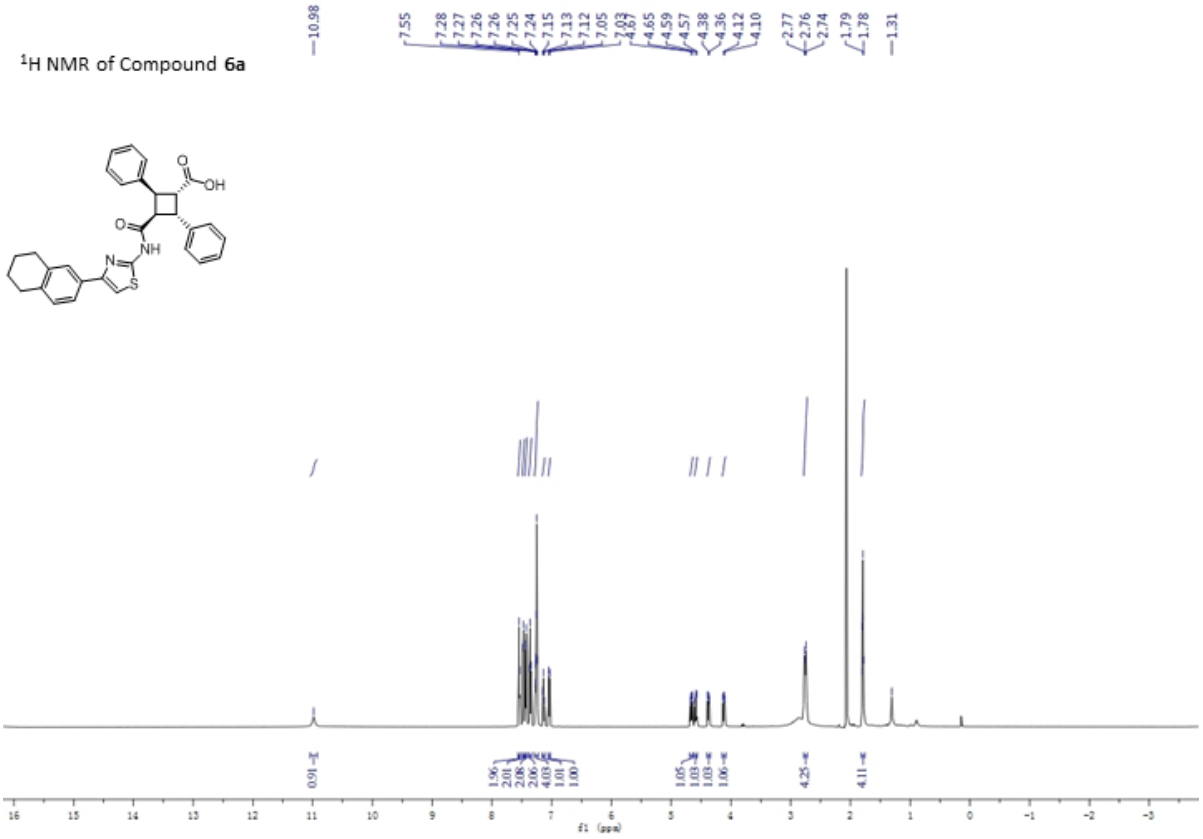
^{1}H NMR of Compound **5e**



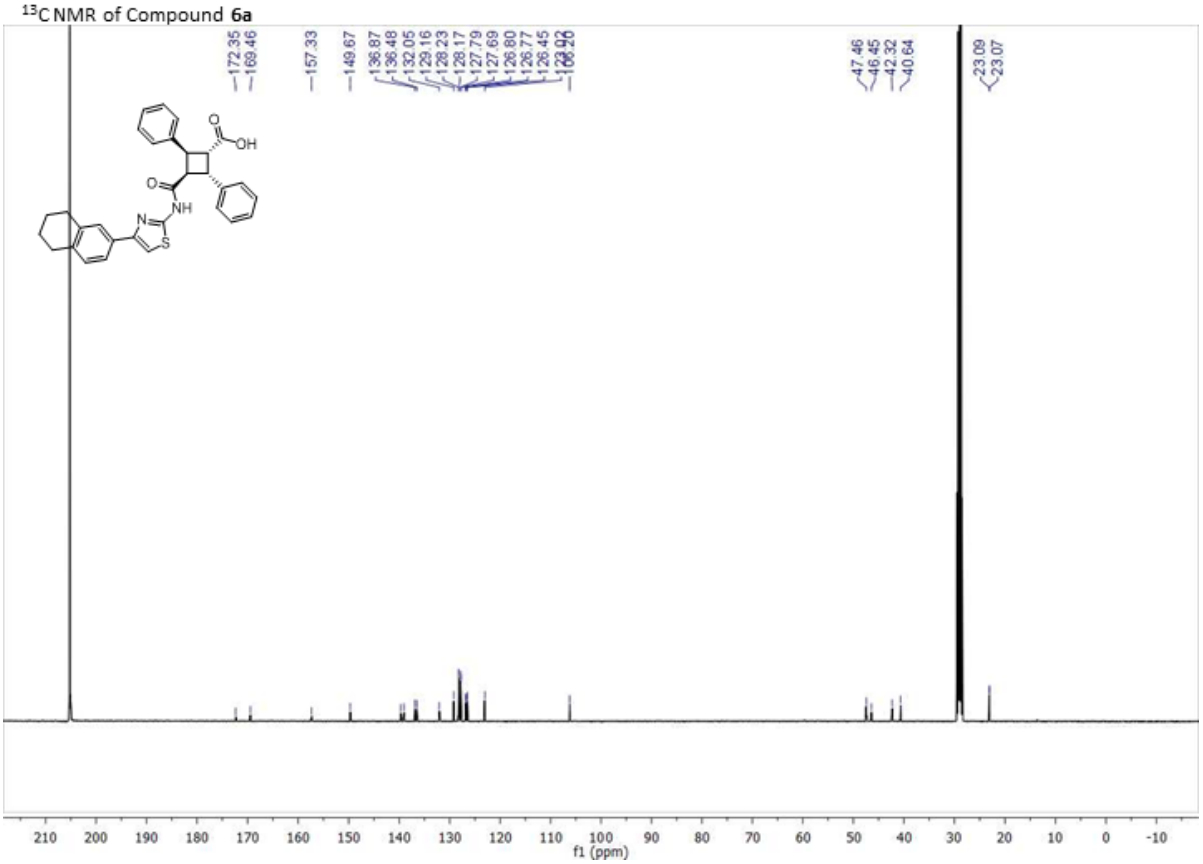
^{13}C NMR of Compound **5e**



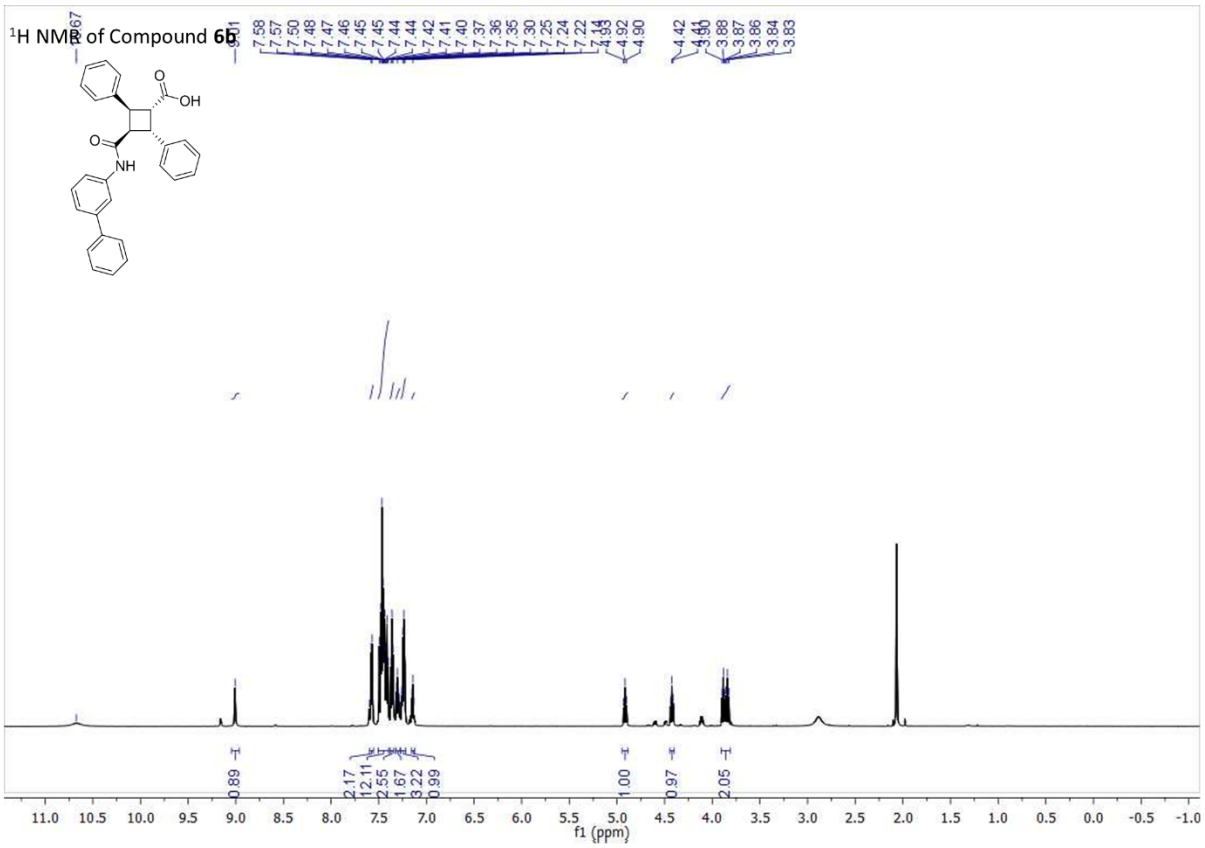
^{1}H NMR of Compound **6a**



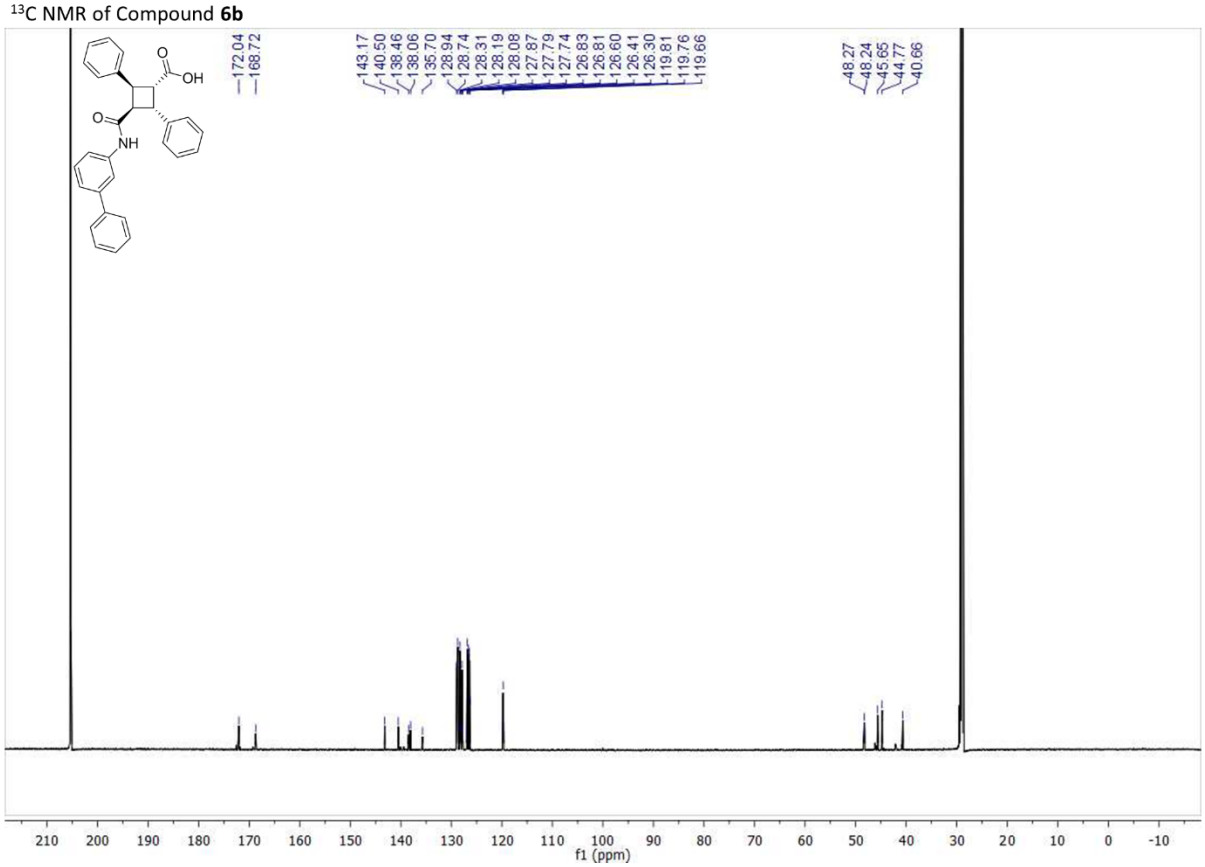
^{13}C NMR of Compound **6a**



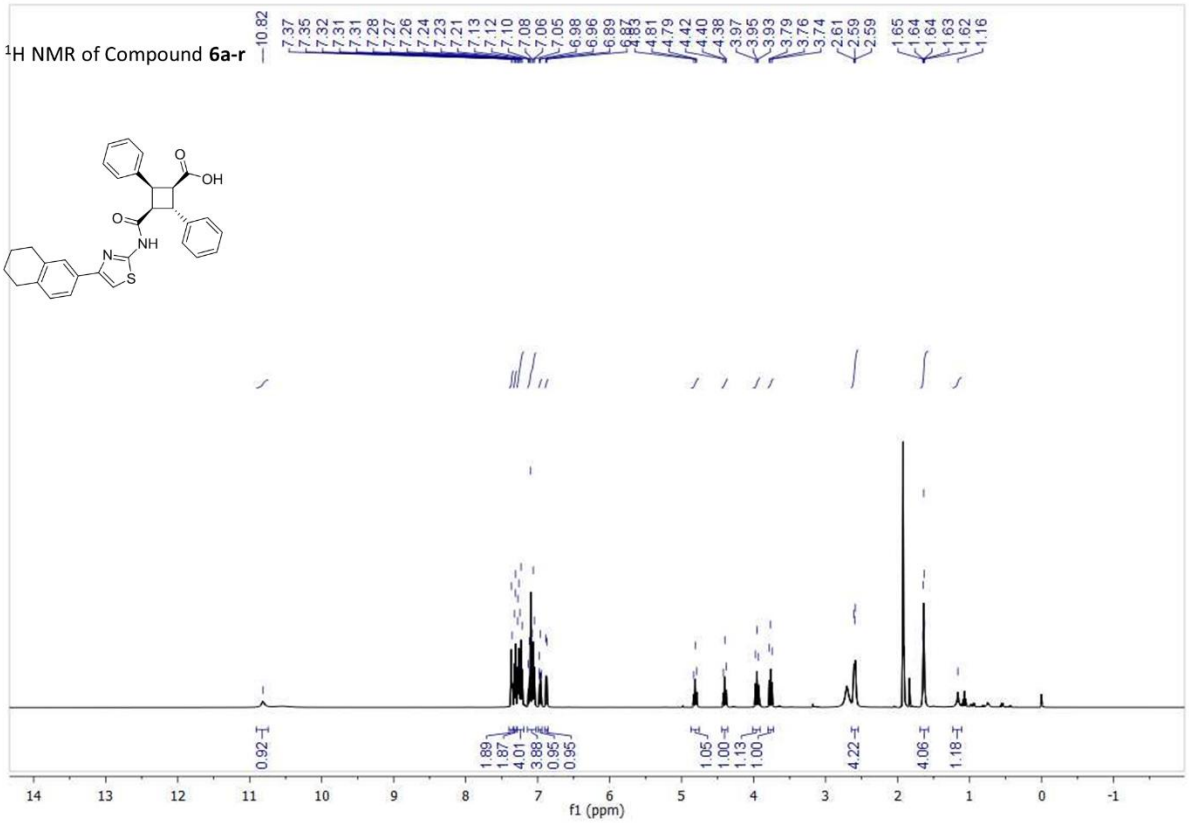
^{1}H NMR of Compound **6b**



^{13}C NMR of Compound **6b**



^{1}H NMR of Compound **6a-r**



^{13}C NMR of Compound **6a-r**