Stilbene Boronic Acids Form a Covalent Bond with Human Transthyretin and Inhibit its Aggregation

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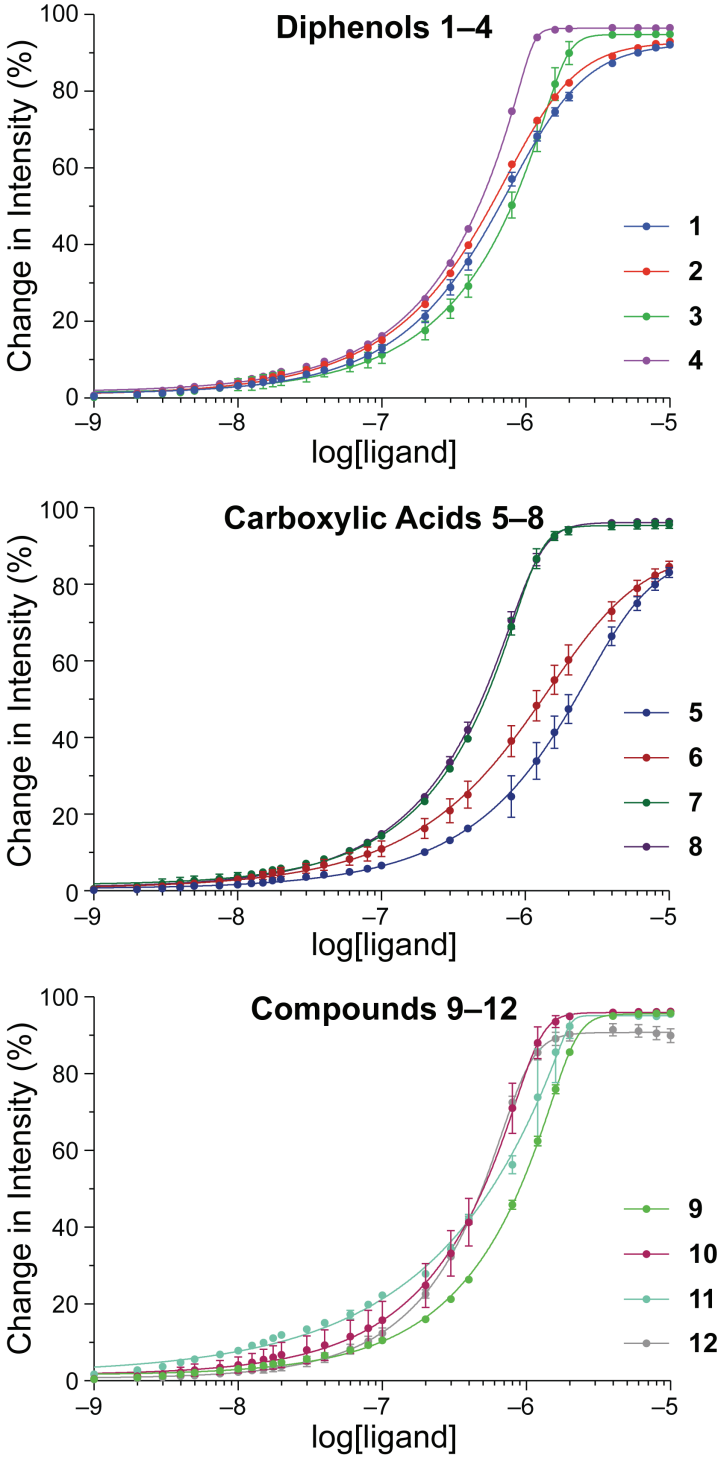


Figure S1. Graphs showing the results of ANS competition assays. (A) Compounds **1**–**4**. (B) Compounds **5**–**8**. (C) Compounds **9**–**12**. Data were fitted to eq 1 to derive values of $K_{d,2}$ (Table 1); R^2 > 0.99 for each dataset.

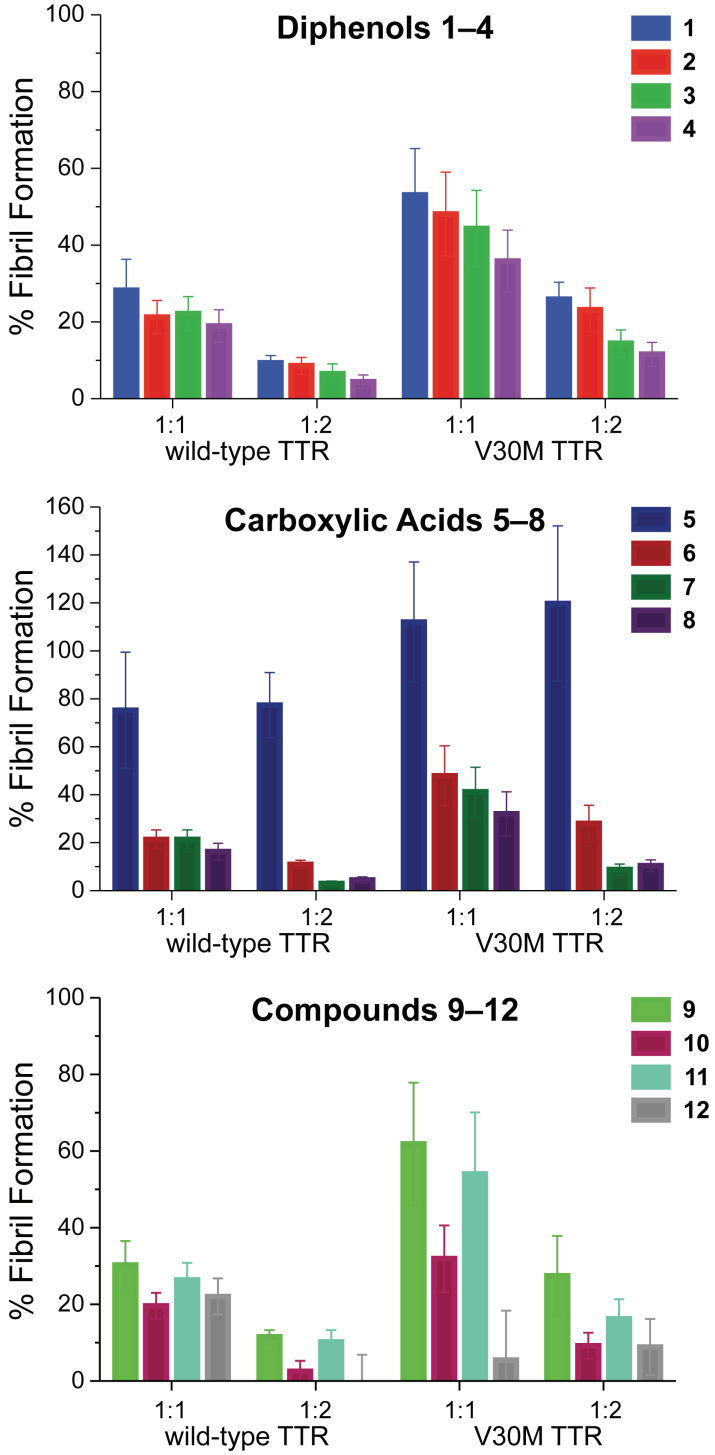


Figure S2. Graphs showing the results of 96-h fibril-formation assays at two different TTR:compound ratios. (A) Compounds **1**–**4**. (B) Compounds **5**–**8**. (C) Compounds **9**–**12**. Error bars represent the standard deviation of 16 measurements propagated through eq 2.

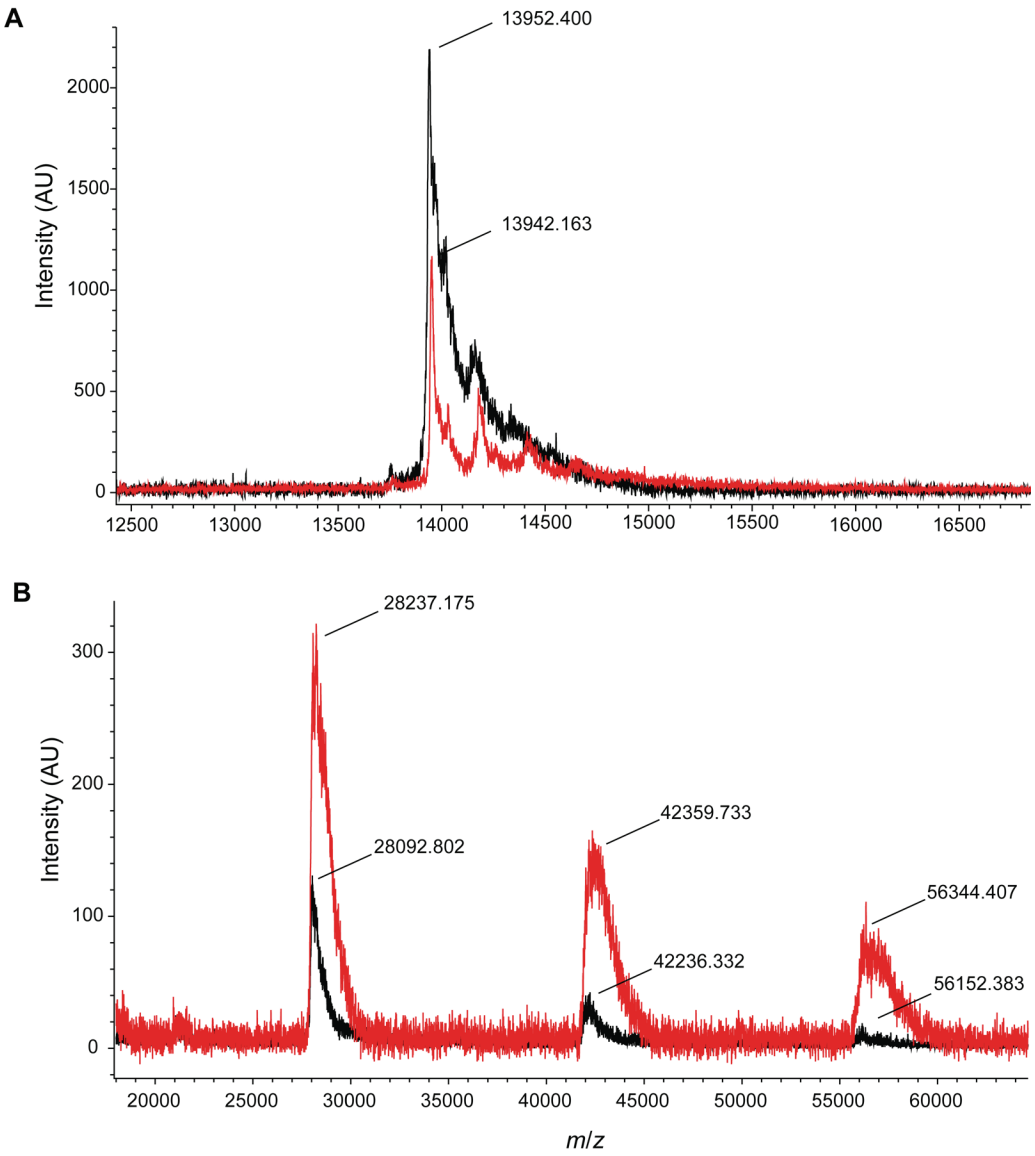
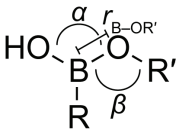


Figure S3. MALDI–TOF mass spectra to probe the reversibility of TTR inhibition. TTR (3.6 μM) was treated with compound **10** (360 μM) (red) or with buffer alone (black), both containing DMF (5% v/v). No significant shift in mass was observed for monomeric TTR (A) or its higher molecular mass oligomers (B), indicating that the TTR·**10** complex dissociates.

Table S1. Bond angles and bond lengths of planar boronic esters in small-molecule crystal structures in the Cambridge Structural Database (CSD) and in protein co-crystal structures reported in this work. The parameter *n* refers to the number of B–OR′ bonds in the structure. The means values of the bond angles *α* and *β*, and the bond length $r_{B–OR'}$ from these small-molecule structures were used in the refinement of X-ray diffraction data from the TTR·**10** and TTR·**11** complexes with the program phenix refine.



CSD entry	*α* (°)	*β* (°)	$r_{B–OR'}$ (Å)	*n*
DOFLIU	124	123	1.37	2
DOFLOA	125	124	1.37	2
DOFLUG	122	123	1.38	4
HOXPOA	120	120	1.37	2
LUKWUK	118	120	1.36	1
NEYVIX	119	121	1.36	1
QEHMAT	119	120	1.35	1
REZYEA	119	122	1.36	4
TOMKAJ	118	112	1.39	2
WUMCAK	118	109	1.37	1
Mean ± SD	120 ± 3	119 ± 5	1.37 ± 0.02	

Ligand	Chain	*α* (°)	*β* (°)	$r_{B–OR'}$ (Å)
10	A	116	109	1.44
10	B	116	108	1.37
11	A	121	116	1.42
11	B	124	109	1.43

Table S2. Crystallographic data collection and refinement statistics for the TTR·**2** complex.

Complex	2
PDB Code	5u48
Data Collection	
X-Ray Source	LS-CAT 21-ID-G
Detector	MAR 300 CCD
Wavelength (Å)	0.97857
Resolution, last shell (Å)	35.5–1.50 (1.55–1.50)
Space group	$P\ 2_1\ 2_1\ 2_1$
Unit cell, *a*, *b*, *c* (Å)	*a* = 43.228, *b* = 84.947
	c = 64.606
Unit cell, *α*, *β*, *γ* (°)	*α* = *β* = *γ* = 90
No. of Reflections	284,040
No. of Unique Reflections	39,026 (1904)
Redundancy (last shell)	7.3 (7.3)
Mean *I*/*σ* (last shell)	28.6 (2.6)
Completeness (last shell)	99.9 (100.0)
R-meas (last shell)	0.056 (0.738)
R-pim (last shell)	0.021 (0.272)
Wilson *B*-factor	18.16
Average Mosaicity (°)	0.2
Refinement	
Working Set (last shell)	35,141 (3422)
Test Set (last shell)	3843 (376)
R_{work} (last shell)	0.178 (0.233)
R_{free} (last shell)	0.205 (0.260)
RMSD of Bond Lengths (Å)	0.007
RMSD of Bond Angles (°)	1.05
Total Number of Atoms	1985
Protein Residues	231
Protein	1826
Ligand	38
Water	121
Average *B*-factor	23.9
Protein	23.4
Ligand	22.4
Water	31.9
Ramachandran Favored, Allowed, Outliers (%) from MolProbity	98.7, 1.3, 0

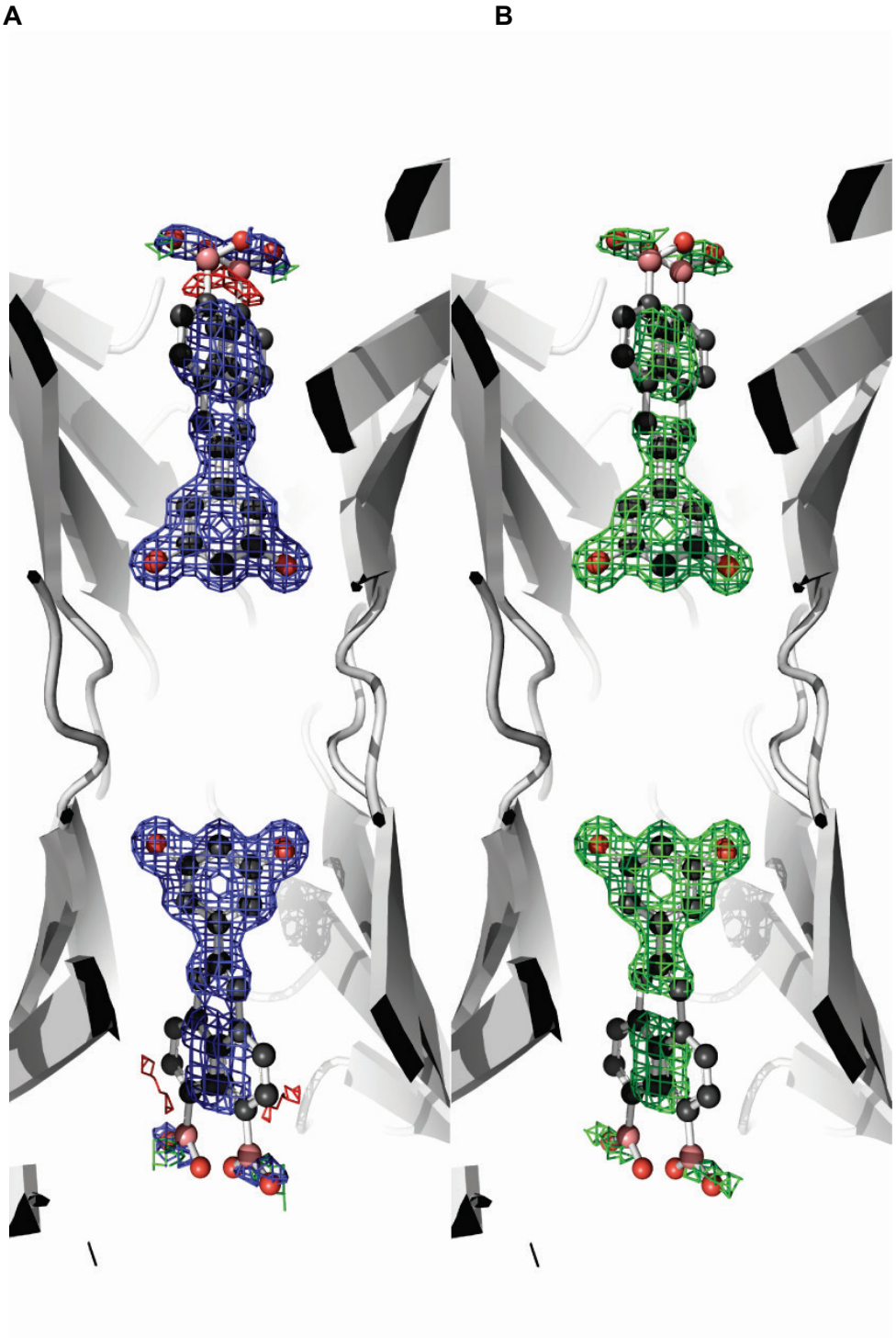


Figure S4. Electron density in the TTR·**2** complex. (A) Final structure. Blue: $2F_o - F_c$ contoured at 1.0σ; red and green: $F_o - F_c$ contoured at –3.0σ and 3.0σ, respectively. (B) Final structure after ligand removal and refinement by simulated annealing. Green: $F_o - F_c$ contoured at 3.0σ.

Table S3. Crystallographic data collection and refinement statistics for the TTR·**3** complex.

Complex	3
PDB Code	5u49
Data Collection	
X-Ray Source	LS-CAT 21-ID-D
Detector	Detris Eiger 9M
Wavelength (Å)	1.239801
Resolution, last shell (Å)	33.0–2.22 (2.30–2.22)
Space group	*I* 2 2 2
Unit cell, *a*, *b*, *c* (Å)	*a* = 44.517, *b* = 65.895
	c = 84.594
Unit cell, *α*, *β*, *γ* (°)	*α* = *β* = *γ* = 90
No. of Reflections	39,109
No. of Unique Reflections	5956 (300)
Redundancy (last shell)	6.6 (4.4)
Mean *I*/*σ* (last shell)	19.2 (2.3)
Completeness (last shell)	98.7 (98.0)
R-meas (last shell)	0.395 (1.722)
R-pim (last shell)	0.151 (0.757)
Wilson *B*-factor	38.3
Average Mosaicity (°)	1.3
Refinement	
Working Set (last shell)	5598 (1311)
Test Set (last shell)	621 (146)
R_{work} (last shell)	0.202 (0.249)
R_{free} (last shell)	0.275 (0.318)
RMSD of Bond Lengths (Å)	0.008
RMSD of Bond Angles (°)	1.04
Total Number of Atoms	925
Protein Residues	116
Protein	896
Ligand	18
Water	11
Average *B*-factor	41.2
Protein	41.3
Ligand	39.5
Water	38.5
Ramachandran Favored, Allowed, Outliers (%) from MolProbity	96.5, 3.5, 0

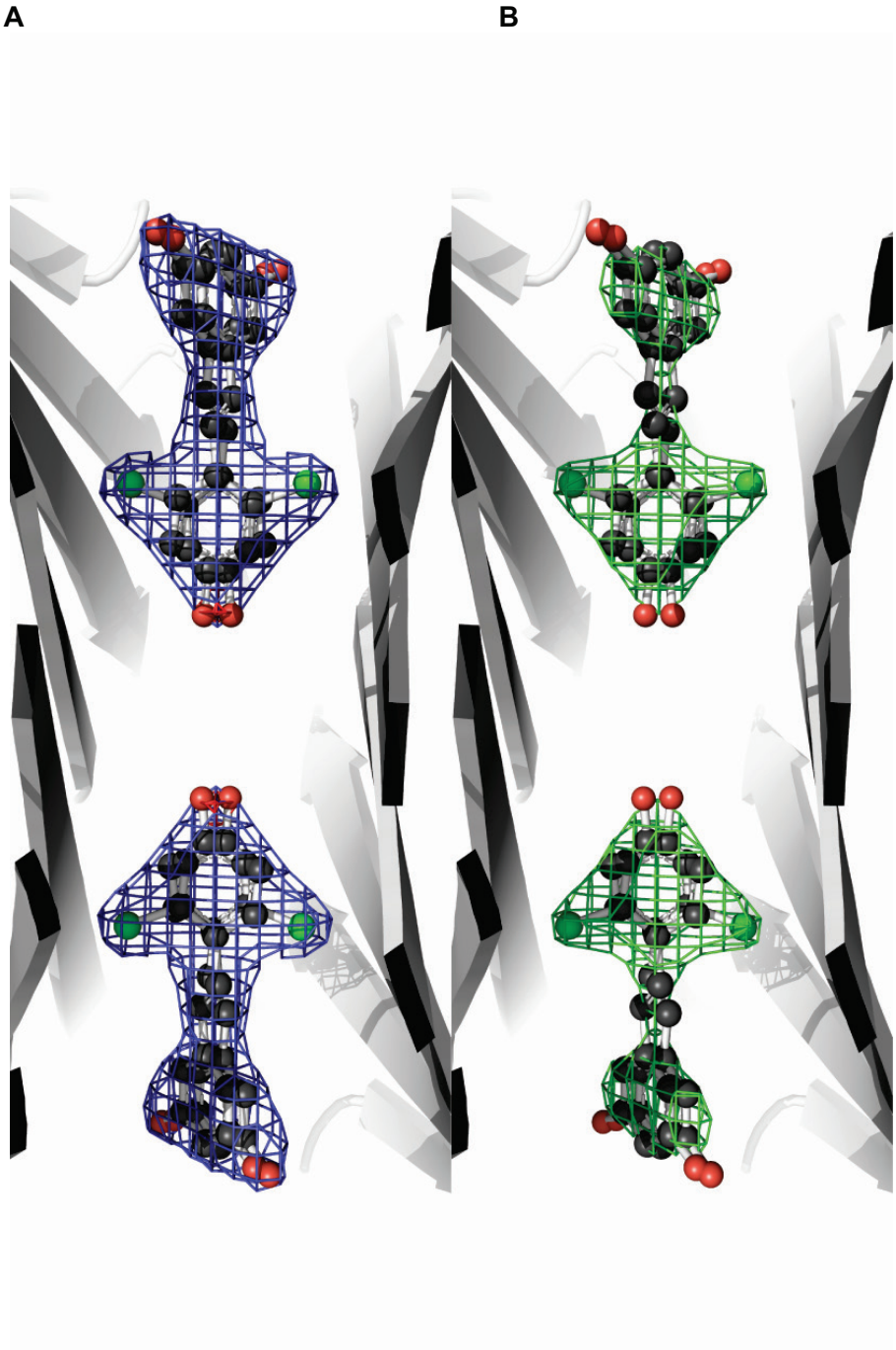


Figure S5. Electron density in the TTR·**3** complex. (A) Final structure. Blue: $2F_o - F_c$ contoured at 1.0σ; red and green: $F_o - F_c$ contoured at –3.0σ and 3.0σ, respectively. (B) Final structure after ligand removal and refinement by simulated annealing. Green: $F_o - F_c$ contoured at 3.0σ.

Table S4. Crystallographic data collection and refinement statistics for the TTR·**4** complex.

Complex	4
PDB Code	5u4a
Data Collection	
X-Ray Source	LS-CAT 21-ID-G
Detector	MAR 300 CCD
Wavelength (Å)	0.97857
Resolution, last shell (Å)	35.5–1.90 (1.96–1.90)
Space group	$P\ 2_1\ 2_1\ 2_1$
Unit cell, *a*, *b*, *c* (Å)	*a* = 42.822, *b* = 84.928
	c = 64.19
Unit cell, *α*, *β*, *γ* (°)	*α* = *β* = *γ* = 90
No. of Reflections	137,456
No. of Unique Reflections	19,212 (936)
Redundancy (last shell)	7.2 (7.2)
Mean *I*/*σ* (last shell)	19.4 (2.3)
Completeness (last shell)	99.8 (100.0)
R-meas (last shell)	0.097 (0.787)
R-pim (last shell)	0.037 (0.289)
Wilson *B*-factor	33.6
Average Mosaicity (°)	1.4
Refinement	
Working Set (last shell)	17,310 (1291)
Test Set (last shell)	1859 (143)
R_{work} (last shell)	0.223 (0.247)
R_{free} (last shell)	0.276 (0.279)
RMSD of Bond Lengths (Å)	0.007
RMSD of Bond Angles (°)	1.03
Total Number of Atoms	1907
Protein Residues	232
Protein	1792
Ligand	40
Water	75
Average *B*-factor	39.0
Protein	38.9
Ligand	32.4
Water	44.6
Ramachandran Favored, Allowed, Outliers (%) from MolProbity	97.4, 2.2, 0.4

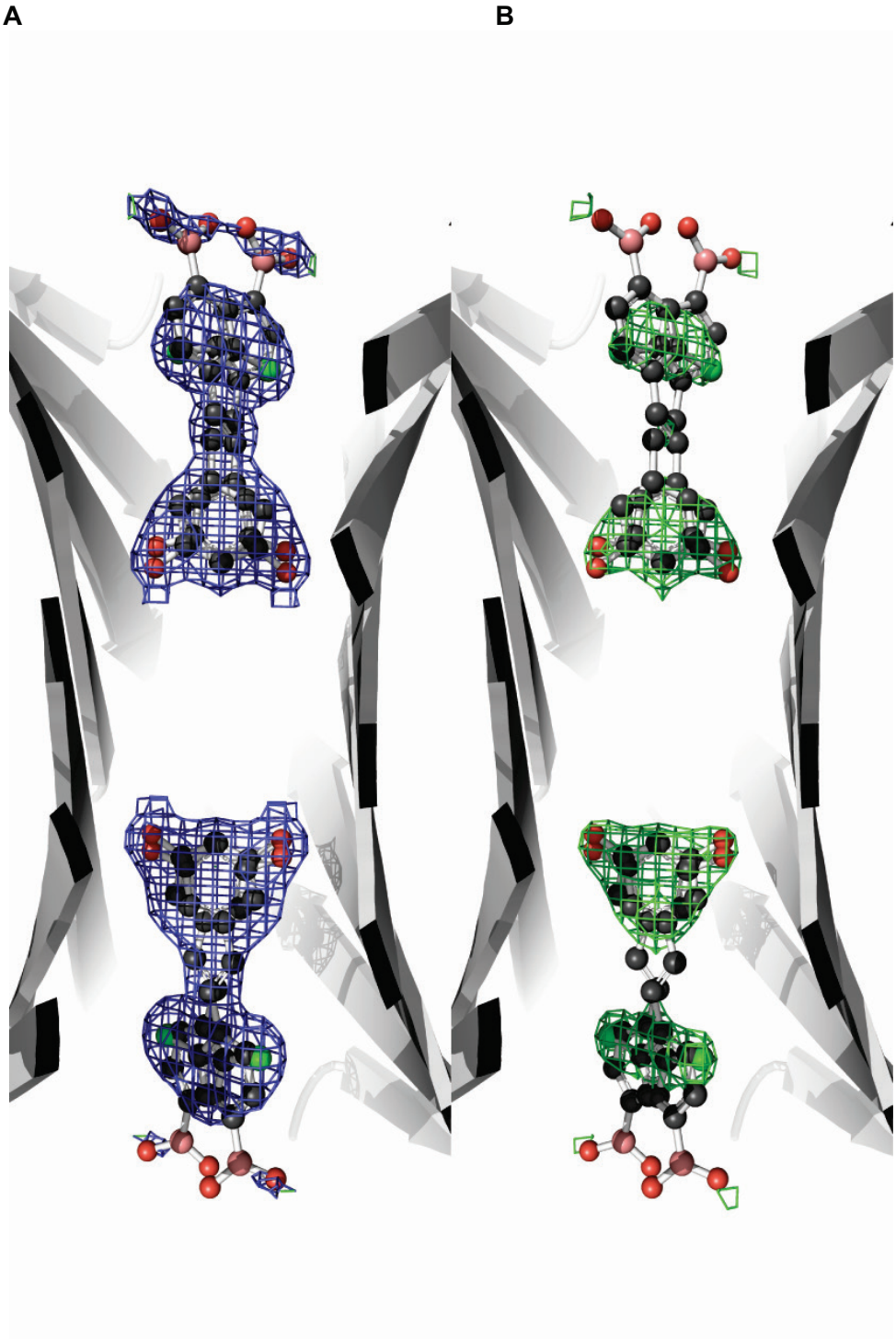


Figure S6. Electron density in the TTR·**4** complex. (A) Final structure. Blue: $2F_o - F_c$ contoured at 1.0σ; red and green: $F_o - F_c$ contoured at –3.0σ and 3.0σ, respectively. (B) Final structure after ligand removal and refinement by simulated annealing. Green: $F_o - F_c$ contoured at 3.0σ.

Table S5. Crystallographic data collection and refinement statistics for the TTR·**5** complex.

Complex	5
PDB Code	5u4b
Data Collection	
X-Ray Source	LS-CAT 21-ID-G
Detector	MAR 300 CCD
Wavelength (Å)	0.97857
Resolution, last shell (Å)	38.5–1.45 (1.5–1.45)
Space group	$P\ 2_1\ 2_1\ 2_1$
Unit cell, *a*, *b*, *c* (Å)	*a* = 43.052, *b* = 85.446
	c = 64.107
Unit cell, *α*, *β*, *γ* (°)	*α* = *β* = *γ* = 90
No. of Reflections	311,252
No. of Unique Reflections	42,801 (2112)
Redundancy (last shell)	7.3 (7.2)
Mean *I*/*σ* (last shell)	25.4 (2.7)
Completeness (last shell)	99.9 (100.0)
R-meas (last shell)	0.065 (0.582)
R-pim (last shell)	0.024 (0.214)
Wilson *B*-factor	15.4
Average Mosaicity (°)	0.2
Refinement	
Working Set (last shell)	38,552 (3756)
Test Set (last shell)	4230 (405)
R_{work} (last shell)	0.186 (0.241)
R_{free} (last shell	0.207 (0.269)
RMSD of Bond Lengths (Å)	0.007
RMSD of Bond Angles (°)	1.03
Total Number of Atoms	2051
Protein Residues	231
Protein	1858
Ligand	36
Water	157
Average *B*-factor	19.6
Protein	18.8
Ligand	27.3
Water	27.2
Ramachandran Favored, Allowed, Outliers (%) from MolProbity	99.2, 0.8, 0

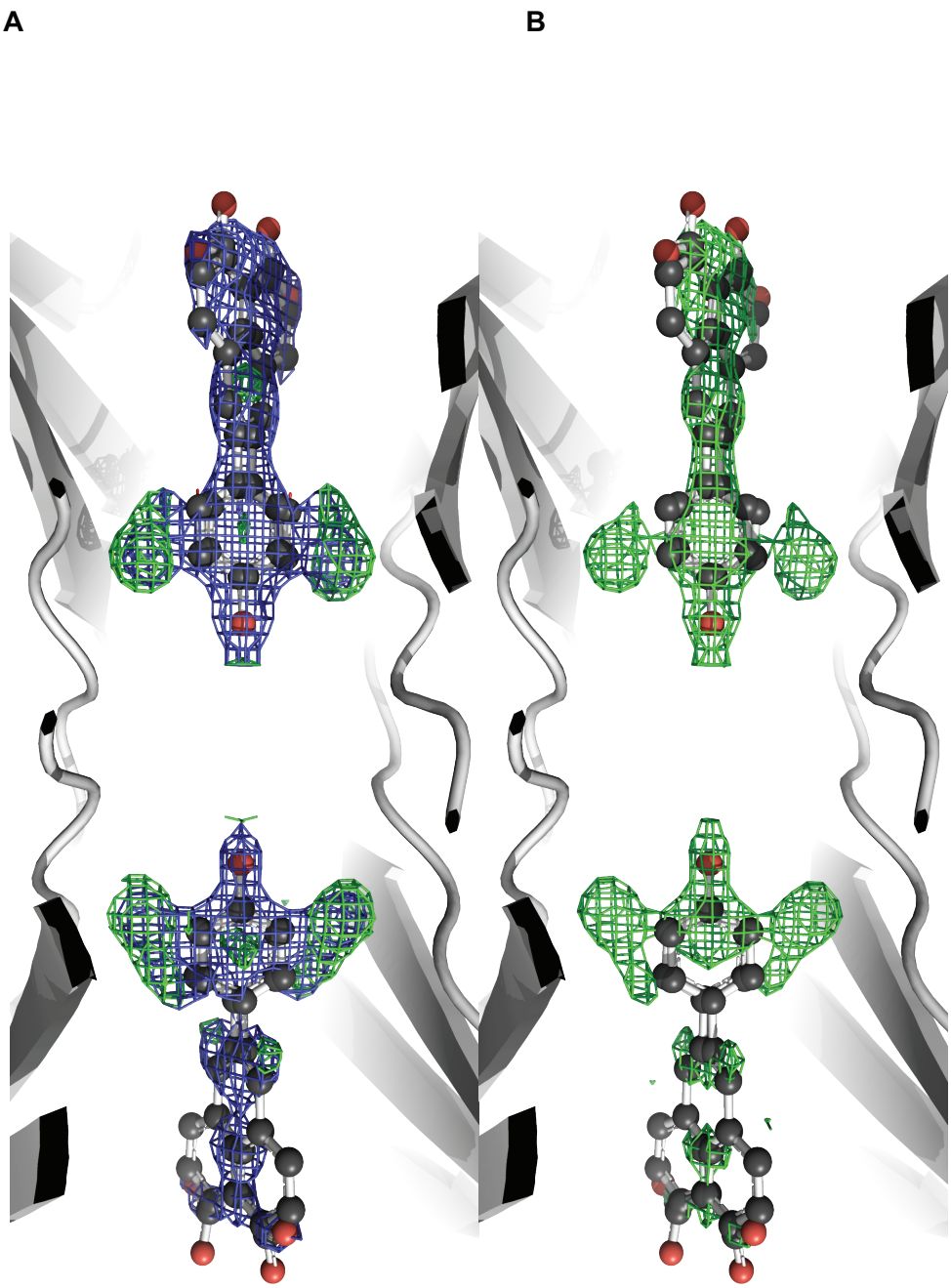


Figure S7. Electron density in the TTR·**5** complex. (A) Final structure. Blue: $2F_o - F_c$ contoured at 1.0σ; red and green: $F_o - F_c$ contoured at –3.0σ and 3.0σ, respectively. (B) Final structure after ligand removal and refinement by simulated annealing. Green: $F_o - F_c$ contoured at 3.0σ.

Table S6. Crystallographic data collection and refinement statistics for the TTR·**6** complex.

Complex	6
PDB Code	5u4c
Data Collection	
X-Ray Source	LS-CAT 21-ID-G
Detector	MAR 300 CCD
Wavelength (Å)	0.97857
Resolution, last shell (Å)	36.0–1.7 (1.76–1.70)
Space group	$P\ 2_1\ 2_1\ 2_1$
Unit cell, *a*, *b*, *c* (Å)	*a* = 42.924, *b* = 85.580
	c = 63.762
Unit cell, *α*, *β*, *γ* (°)	*α* = *β* = *γ* = 90
No. of Reflections	191,623
No. of Unique Reflections	26,541 (1303)
Redundancy (last shell)	7.2 (7.1)
Mean *I*/*σ* (last shell)	23.9 (2.0)
Completeness (last shell)	99.6 (99.1)
R-meas (last shell)	0.065 (0.818)
R-pim (last shell)	0.024 (0.301)
Wilson *B*-factor	19.4
Average Mosaicity (°)	0.6
Refinement	
Working Set (last shell)	23,900 (2334)
Test Set (last shell)	2593 (224)
R_{work} (last shell)	0.176 (0.225)
R_{free} (last shell)	0.204 (0.271)
RMSD of Bond Lengths (Å)	0.007
RMSD of Bond Angles (°)	1.061
Total Number of Atoms	2043
Protein Residues	231
Protein	1869
Ligand	40
Water	134
Average *B*-factor	23.8
Protein	23.7
Ligand	30.8
Water	30.1
Ramachandran Favored, Allowed, Outliers (%) from MolProbity	97.9, 1.7, 0.4

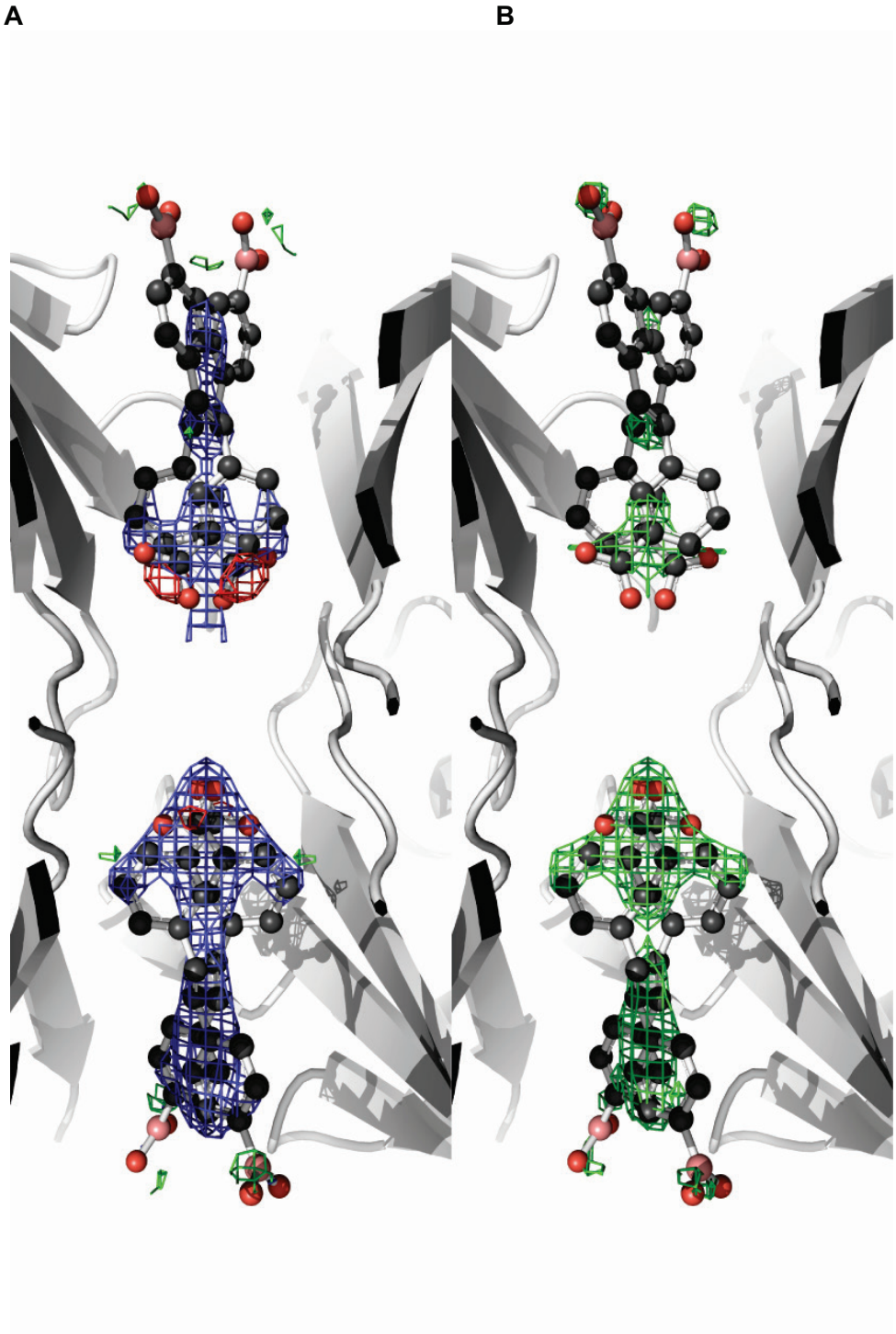


Figure S8. Electron density in the TTR·**6** complex. (A) Final structure. Blue: $2F_o - F_c$ contoured at 1.0σ; red and green: $F_o - F_c$ contoured at –3.0σ and 3.0σ, respectively. (B) Final structure after ligand removal and refinement by simulated annealing. Green: $F_o - F_c$ contoured at 3.0σ.

Table S7. Crystallographic data collection and refinement statistics for the TTR·**7** complex.

Complex	7
PDB Code	5u4d
Data Collection	
X-Ray Source	LS-CAT 21-ID-F
Detector	MAR 225 CCD
Wavelength (Å)	0.97872
Resolution, last shell (Å)	38.5–1.55 (1.60–1.55)
Space group	$P\ 2_1\ 2_1\ 2_1$
Unit cell, *a*, *b*, *c* (Å)	*a* = 43.207, *b* = 84.814
	c = 64.618
Unit cell, *α*, *β*, *γ* (°)	*α* = *β* = *γ* = 90
No. of Reflections	21,6074
No. of Unique Reflections	35,258 (1735)
Redundancy (last shell)	6.1 (5.2)
Mean *I*/*σ* (last shell)	23.7 (2.1)
Completeness (last shell)	99.8 (99.5)
R-meas (last shell)	0.072 (0.675)
R-pim (last shell)	0.028 (0.291)
Wilson *B*-factor	19.2
Average Mosaicity (°)	0.2
Refinement	
Working Set (last shell)	31740 (3067)
Test Set (last shell)	3474 (364)
R_{work} (last shell)	0.206 (0.303)
R_{free} (last shell)	0.243 (0.356)
RMSD of Bond Lengths (Å)	0.007
RMSD of Bond Angles (°)	1.038
Total Number of Atoms	1989
Protein Residues	231
Protein	1821
Ligand	38
Water	130
Average *B*-factor	26.4
Protein	25.8
Ligand	26.6
Water	34.1
Ramachandran Favored, Allowed, Outliers (%) from MolProbity	97.5, 2.5, 0

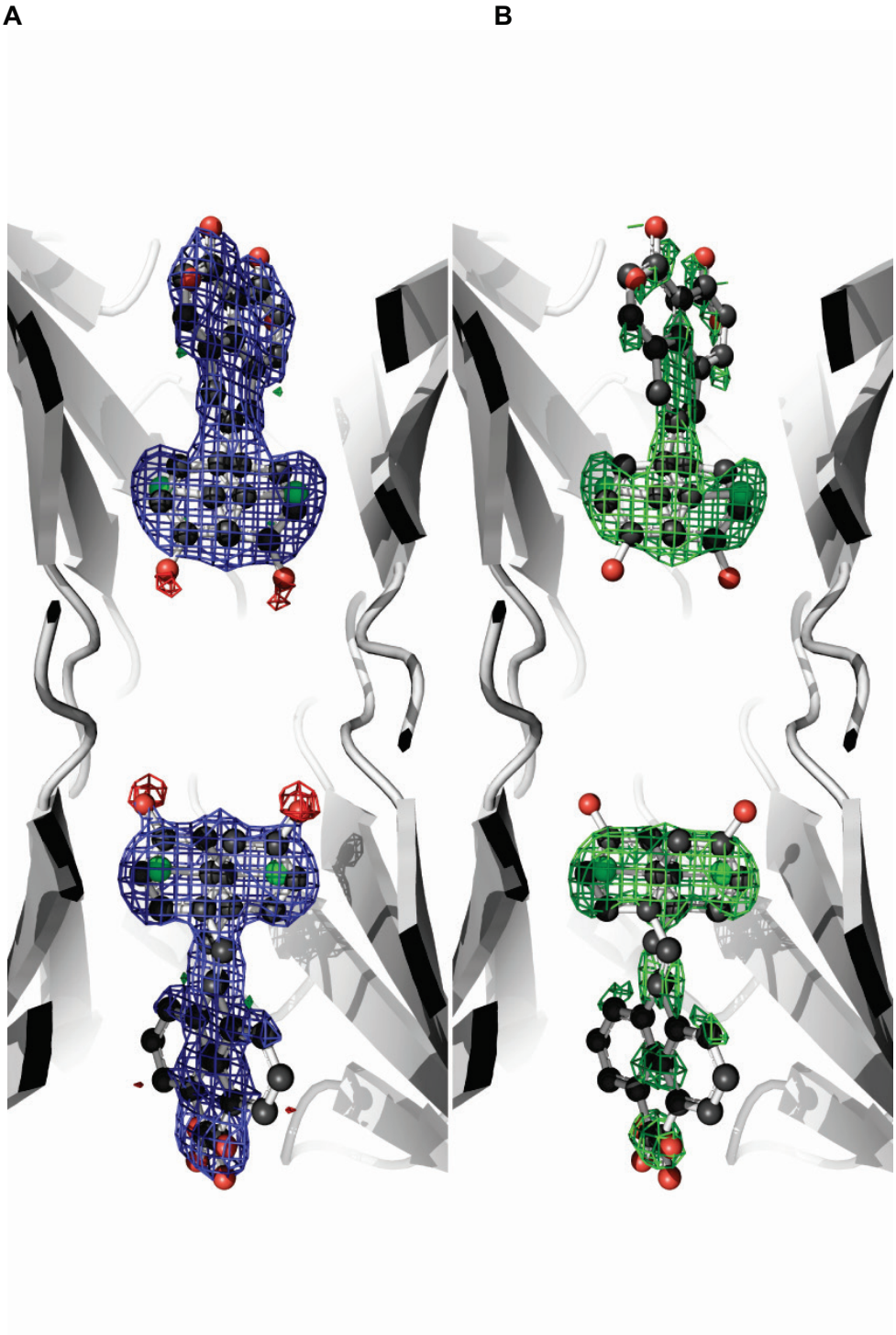


Figure S9. Electron density in the TTR·**7** complex. (A) Final structure. Blue: $2F_o - F_c$ contoured at 1.0σ; red and green: $F_o - F_c$ contoured at –3.0σ and 3.0σ, respectively. (B) Final structure after ligand removal and refinement by simulated annealing. Green: $F_o - F_c$ contoured at 3.0σ.

Table S8. Crystallographic data collection and refinement statistics for the TTR·**8** complex.

Complex	8
PDB Code	5u4e
Data Collection	
X-Ray Source	LS-CAT 21-ID-G
Detector	MAR 300 CCD
Wavelength (Å)	0.97857
Resolution, last shell (Å)	26.0–1.45 (1.50–1.45)
Space group	$P\ 2_1\ 2_1\ 2_1$
Unit cell, *a*, *b*, *c* (Å)	*a* = 43.029, *b* = 85.861
	c = 63.831
Unit cell, *α*, *β*, *γ* (°)	*α* = *β* = *γ* = 90
No. of Reflections	309,849
No. of Unique Reflections	42,788 (2094)
Redundancy (last shell)	7.2 (7.1)
Mean *I*/*σ* (last shell)	30.2 (2.5)
Completeness (last shell)	100.0 (99.9)
R-meas (last shell)	0.055 (0.659)
R-pim (last shell)	0.20 (0.243)
Wilson *B*-factor	15.4
Average Mosaicity (°)	0.4
Refinement	
Working Set (last shell)	38,504 (3747)
Test Set (last shell)	4229 (405)
R_{work} (last shell)	0.18 (0.259)
R_{free} (last shell)	0.198 (0.290)
RMSD of Bond Lengths (Å)	0.007
RMSD of Bond Angles (°)	1.163
Total Number of Atoms	2154
Protein Residues	231
Protein	1901
Ligand	84
Water	169
Average *B*-factor	19.8
Protein	19.2
Ligand	20.1
Water	28.6
Ramachandran Favored, Allowed, Outliers (%) from MolProbity	98.4, 1.2, 0.4

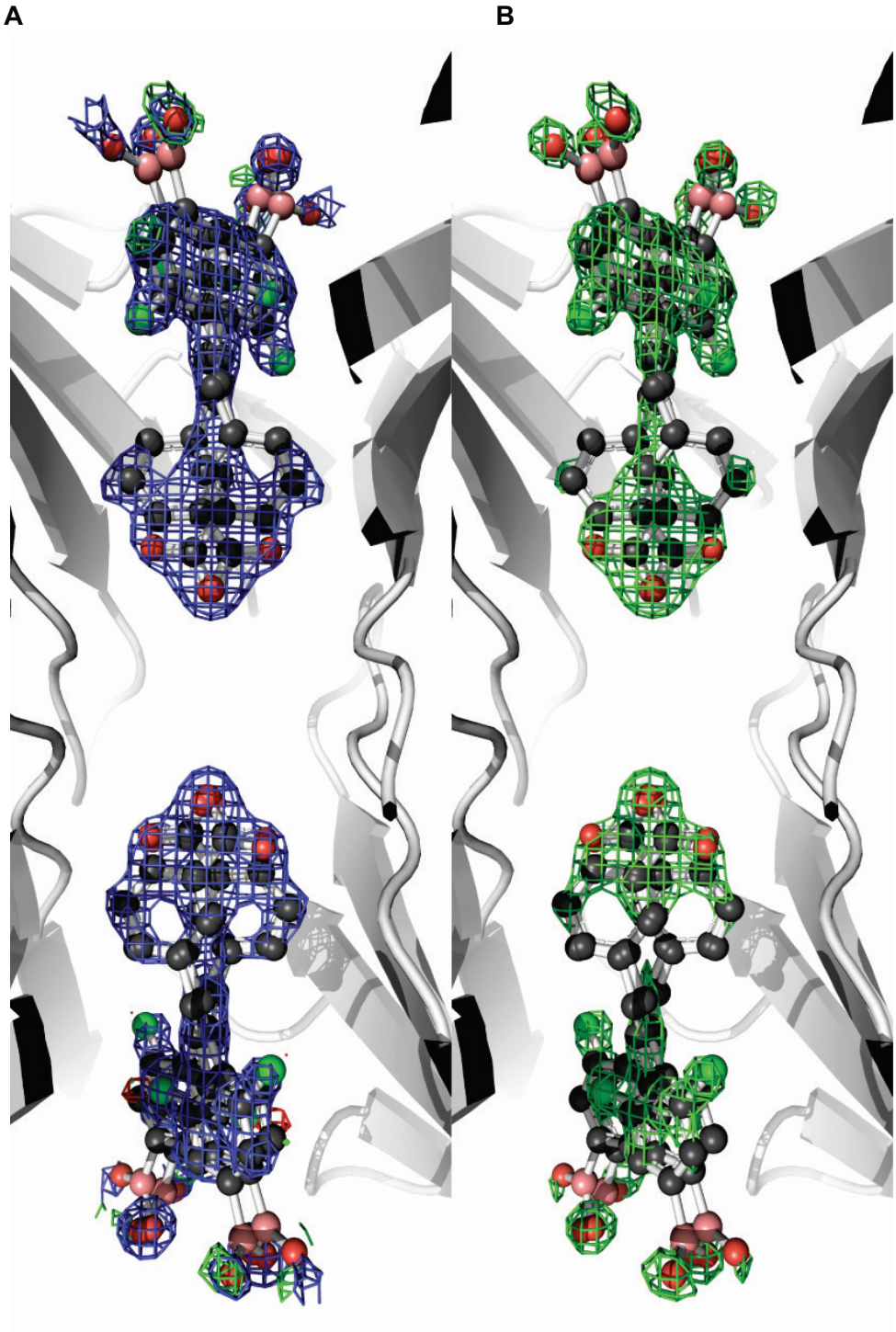


Figure S10. Electron density in the TTR·**8** complex. (A) Final structure. Blue: $2F_o - F_c$ contoured at 1.0σ; red and green: $F_o - F_c$ contoured at –3.0σ and 3.0σ, respectively. (B) Final structure after ligand removal and refinement by simulated annealing. Green: $F_o - F_c$ contoured at 3.0σ.

Table S9. Crystallographic data collection and refinement statistics for the TTR·**10** complex.

Complex	10
PDB Code	5u4f
Data Collection	
X-Ray Source	LS-CAT 21-ID-D
Detector	Detris Eiger 9M
Wavelength (Å)	1.239801
Resolution, last shell (Å)	38.5–1.50 (1.55–1.50)
Space group	$P\ 2_1\ 2_1\ 2_1$
Unit cell, *a*, *b*, *c* (Å)	*a* = 42.920, *b* = 85.223
	c = 63.942
Unit cell, *α*, *β*, *γ* (°)	*α* = *β* = *γ* = 90
No. of Reflections	228,243
No. of Unique Reflections	38,097 (1877)
Redundancy (last shell)	6.0 (6.1)
Mean *I*/*σ* (last shell)	26.3 (3.9)
Completeness (last shell)	99.5 (99.6)
R-meas (last shell)	0.089 (0.466)
R-pim (last shell)	0.035 (0.184)
Wilson B-factor	22.22
Average Mosaicity (°)	0.6
Refinement	
Working Set (last shell)	36,057 (3506)
Test Set (last shell)	2000 (195)
R_{work} (last shell)	0.193 (0.247)
R_{free} (last shell)	0.220 (0.300)
RMSD of Bond Lengths (Å)	0.007
RMSD of Bond Angles (°)	1.12
Total Number of Atoms	1977
Protein Residues	231
Protein	1812
Ligand	42
Water	123
Average B-factor	26.9
Protein	26.4
Ligand	29.3
Water	35.0
Ramachandran Favored, Allowed, Outliers (%) from MolProbity	98.7, 1.3, 0

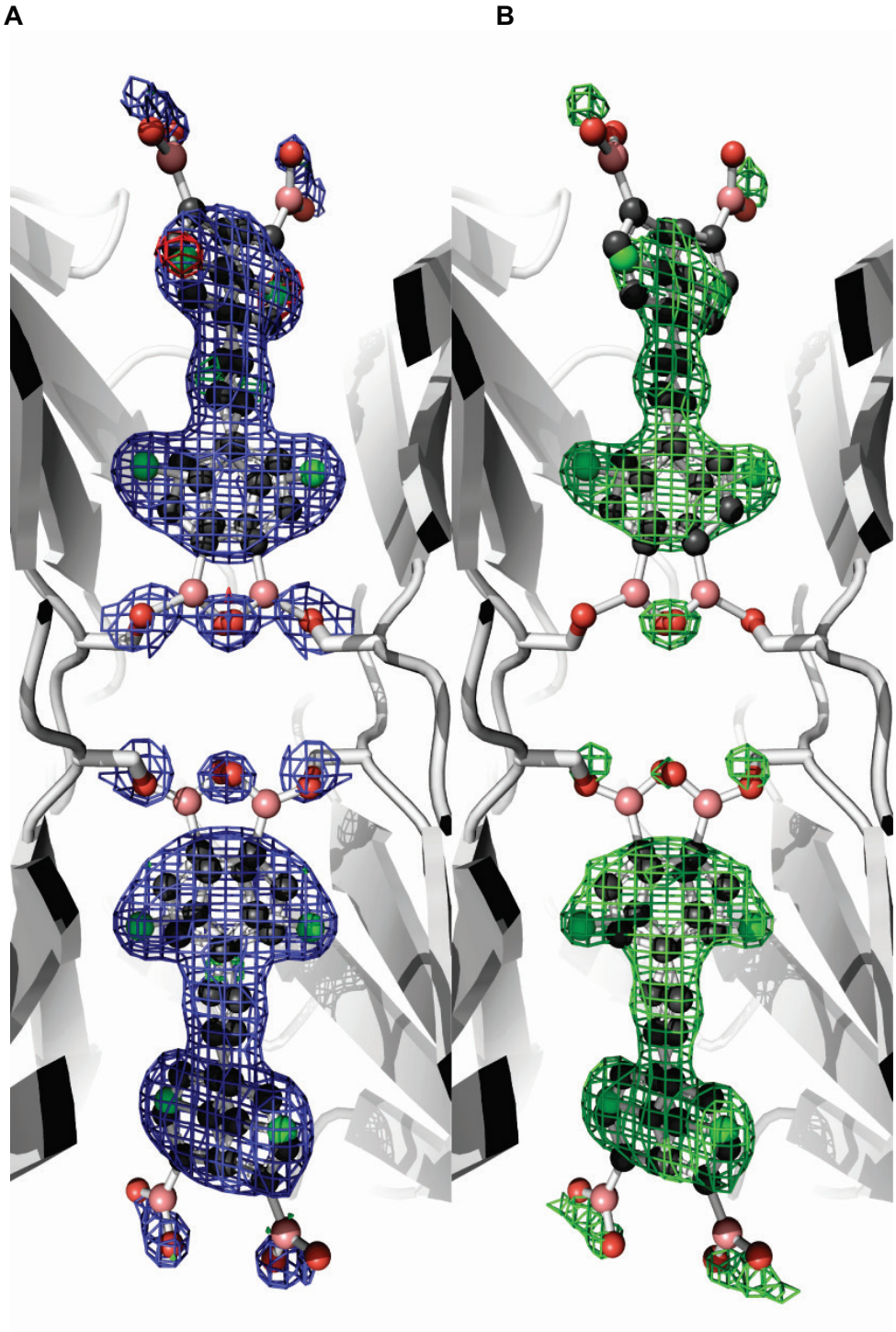


Figure S11. Electron density in the TTR·**10** complex. (A) Final structure. Blue: $2F_o - F_c$ contoured at 1.0σ; red and green: $F_o - F_c$ contoured at –3.0σ and 3.0σ, respectively. (B) Final structure after ligand removal and refinement by simulated annealing. Green: $F_o - F_c$ contoured at 3.0σ.

Table S10. Crystallographic data collection and refinement statistics for the TTR·**11** complex.

Complex	11
PDB Code	5u4g
Data Collection	
X-Ray Source	LS-CAT 21-ID-F
Detector	MAR 225 CCD
Wavelength (Å)	0.97872
Resolution, last shell (Å)	38.5–1.8 (1.86–1.80)
Space group	$P\ 2_1\ 2_1\ 2_1$
Unit cell, *a*, *b*, *c* (Å)	*a* = 43.019, *b* = 85.118
	c = 64.023
Unit cell, *α*, *β*, *γ* (°)	α = *β* = *γ* = 90
No. of Reflections	163,190
No. of Unique Reflections	22,450 (1087)
Redundancy (last shell)	7.3 (7.3)
Mean *I*/*σ* (last shell)	29.4 (3.1)
Completeness (last shell)	99.7 (99.4)
R-meas (last shell)	0.057 (0.513)
R-pim (last shell)	0.021 (0.187)
Wilson *B*-factor	22.8
Average Mosaicity (°)	0.6
Refinement	
Working Set (last shell)	20,232 (1898)
Test Set (last shell)	2189 (199)
R_{work} (last shell)	0.188 (0.246)
R_{free} (last shell	0.223 (0.281)
RMSD of Bond Lengths (Å)	0.009
RMSD of Bond Angles (°)	1.207
Total Number of Atoms	1947
Protein Residues	231
Protein	1799
Ligand	40
Water	108
Average *B*-factor	27.6
Protein	27.3
Ligand	30.5
Water	32.6
Ramachandran Favored, Allowed, Outliers (%) from MolProbity	97.9, 1.7, 0.4

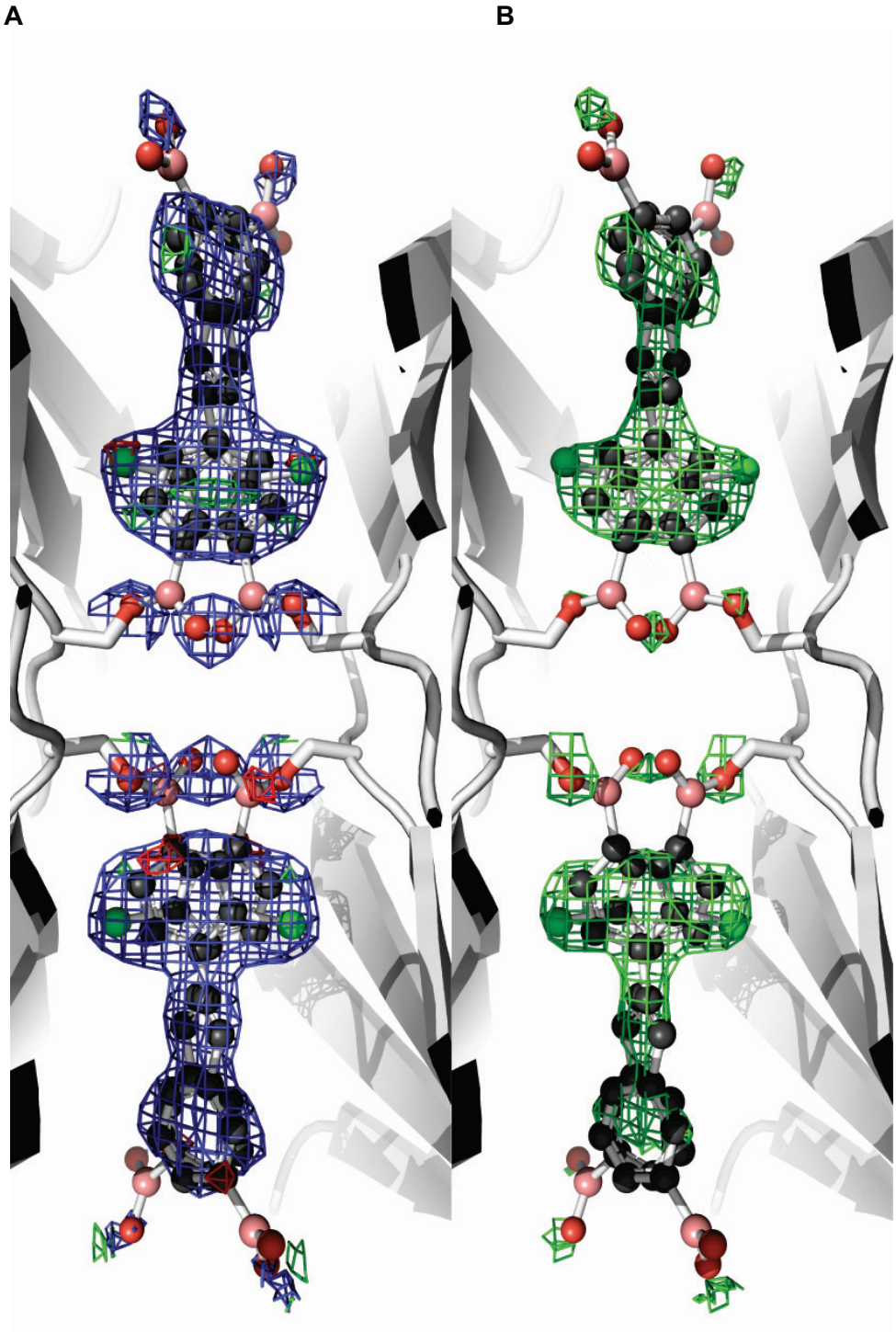


Figure S12. Electron density in the TTR·**11** complex. (A) Final structure. Blue: $2F_o - F_c$ contoured at 1.0σ; red and green: $F_o - F_c$ contoured at –3.0σ and 3.0σ, respectively. (B) Final structure after ligand removal and refinement by simulated annealing. Green: $F_o - F_c$ contoured at 3.0σ.

Table S11. Non-covalent interactions and distances in TTR·ligand complexes.

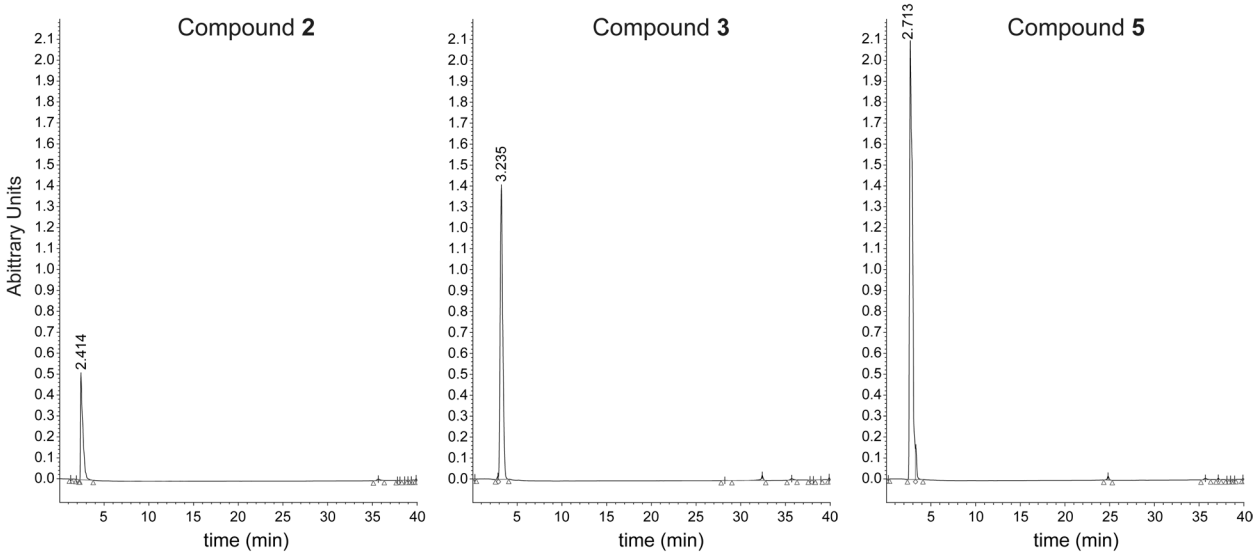
Ligand	Interaction type	Ligand atom	Protein atom	Distance (Å)
2	Dative	B01/A	NZ, A/15 Lys/A	2.8
2	Dative	B01/B	NZ, A/15 Lys/B	3.2
2	Dative	Average	—	3.0
2	Hydrogen bond	O04/A	NZ, A/15 Lys′/A	2.6
2	Hydrogen bond	O03/B	NZ, A/15 Lys′/B	2.2
2	Hydrogen bond	Average	—	2.4
2	Hydrogen bond	O02/A	OG,A/117 Ser/A	2.7
2	Hydrogen bond	O02/A	OG,B/117 Ser/A	3.0
2	Hydrogen bond	O01/A	OG,A/117 Ser′/A	2.7
2	Hydrogen bond	O01/A	OG,B/117 Ser′/A	2.7
2	Hydrogen bond	O02/A	OG,A/117 Ser/B	3.0
2	Hydrogen bond	O02/A	OG,B/117 Ser/B	2.7
2	Hydrogen bond	O01/A	OG,A/117 Ser′/B	2.9
2	Hydrogen bond	O01/A	OG,B/117 Ser′/B	2.6
2	Hydrogen bond	Average	—	2.8
3	Hydrogen bond	O02/A	OG,A/117 Ser/A	2.4
4	Dative	B01/A	NZ, A/15 Lys/A	3.4
4	Dative	B01/B	NZ, A/15 Lys/B	4.4
4	Dative	Average	—	3.9
4	Hydrogen bond	O03/A	NZ, A/15 Lys′/A	3.4
4	Hydrogen bond	O03/B	NZ, A/15 Lys′/B	3.0
4	Hydrogen bond	Average	—	3.2
4	Hydrogen bond	O01/A	OG,A/117 Ser/A	2.2
4	Hydrogen bond	O21/A	OG,A/117 Ser′/A	3.0
4	Hydrogen bond	O02/B	OG,A/117 Ser/B	2.1
4	Hydrogen bond	O01/B	OG,A/117 Ser′/B	2.8
4	Hydrogen bond	Average	—	2.5
5	Hydrogen bond	O01,A/A	OG,A/117 Ser′/B	2.7
5	Hydrogen bond	O01,A/A	OG,B/117 Ser′/B	2.9
5	Hydrogen bond	O01,B/A	OG,A/117 Ser′/B	2.4
5	Hydrogen bond	O01,B/A	OG,B/117 Ser′/B	2.5
5	Hydrogen bond	O01,A/B	OG,A/117 Ser′/A	3.0
5	Hydrogen bond	O01,A/B	OG,A/117 Ser′/A	2.6
5	Hydrogen bond	O01,B/B	OG,A/117 Ser′/A	3.3
5	Hydrogen bond	O01,B/B	OG,A/117 Ser′/A	2.8
5	Hydrogen bond	Average	—	2.8
5	Hydrogen bond	O03/B	NZ, A/15 Lys/A	2.5
5	Hydrogen bond	O02/B	NZ, A/15 Lys′/A	3.6
5	Hydrogen bond	Average	—	3.1
6	Dative	B01/A	NZ, A/15 Lys/A	2.9
6	Dative	B01/B	NZ, A/15 Lys′/B	3.0
6	Hydrogen bond	Average	—	3.0
6	Hydrogen bond	O02/A	NZ, A/15 Lys′/A	3.0
6	Hydrogen bond	O01/B	NZ, A/15 Lys/B	4.0
6	Hydrogen bond	Average	—	3.5
6	Hydrogen bond	O03/A	OG,A/117 Ser′/A	3.1
6	Hydrogen bond	O03/A	OG,B/117 Ser′/A	2.9
6	Hydrogen bond	O04/A	OG,A/117 Ser′/A	2.7

6	Hydrogen bond	O04/A	OG,B/117 Ser′/A	2.3
6	Hydrogen bond	O03/B	OG,A/117 Ser/B	3.0
6	Hydrogen bond	O03/B	OG,B/117 Ser/B	3.1
6	Hydrogen bond	O04/B	OG,A/117 Ser/B	2.4
6	Hydrogen bond	O04/B	OG,B/117 Ser/B	2.5
6	Hydrogen bond	Average	—	2.8
7	Hydrogen bond	O03/A	OG, A/117 Ser′/A	2.2
7	Hydrogen bond	O03/B	OG, A/117 Ser/B	2.3
7	Hydrogen bond	Average	—	2.3
7	Hydrogen bond	O01/A	NZ, A/15 Lys/A	2.7
7	Hydrogen bond	O02/A	NZ, A/15 Lys′/A	2.3
7	Hydrogen bond	Average	—	2.5
8	Dative	B01,A/A	NZ, A/15 Lys/A	2.9
8	Dative	B01,A/B	NZ, A/15 Lys′/B	2.9
8	Cative	Average	—	2.9
8	Hydrogen bond	O02,A/A	NZ, A/15 Lys′/A	3.0
8	Hydrogen bond	O01/B	NZ, A/15 Lys/B	3.0
8	Hydrogen bond	Average	—	3.0
8	Hydrogen bond	O03/A	OG,A/117 Ser′/A	2.9
8	Hydrogen bond	O03/A	OG,B/117 Ser′/A	2.6
8	Hydrogen bond	O04/A	OG,A/117 Ser′/A	2.7
8	Hydrogen bond	O04/A	OG,B/117 Ser′/A	3.0
8	Hydrogen bond	O03/B	OG,A/117 Ser/B	2.8
8	Hydrogen bond	O03/B	OG,B/117 Ser/B	3.0
8	Hydrogen bond	O04/B	OG,A/117 Ser/B	2.5
8	Hydrogen bond	O04/B	OG,B/117 Ser/B	2.7
8	Hydrogen bond	Average	—	2.8
10	Dative	B02/A	NZ, A/15 Lys/A	3.5
10	Hydrogen bond	O03/A	NZ, A/15 Lys′/A	3.6
10	Hydrogen bond	O02/A	NZ, A/15 Lys′/A	2.7
10	Hydrogen bond	O03/B	NZ, A/15 Lys′/B	2.6
10	Hydrogen bond	Average	—	2.7
11	Dative	B01/A	NZ, A/15 Lys/A	3.2
11	Hydrogen bond	O02/A	OG,B/117 Ser′/A	2.8
11	Hydrogen bond	O/04/B	OG,B/117 Ser′/B	3.0
11	Hydrogen bond	Average	—	2.9

Table S12. Observed *σ*-hole bond lengths and bond angles in TTR·ligand complexes

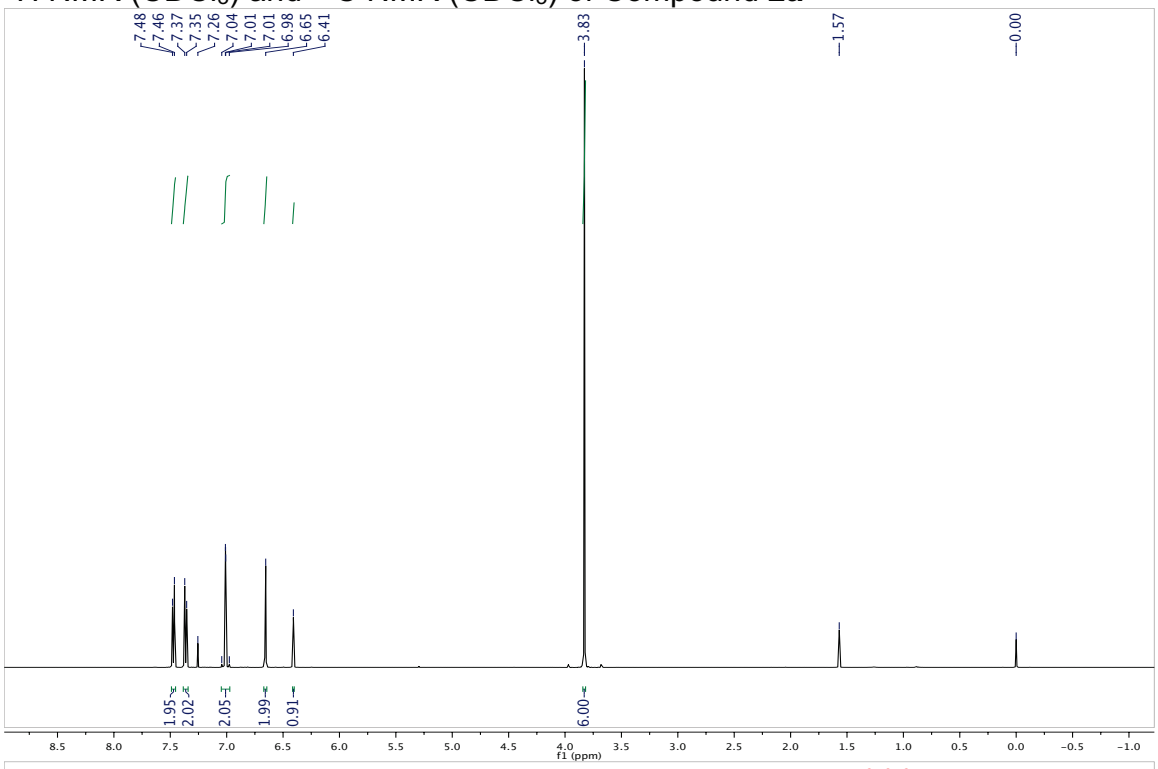
Ligand	Ligand atom	Protein residue	$r_{Cl\cdots O}$ (Å)	$\theta_{C-Cl\cdots O}$ (°)	$\theta_{Cl\cdots O=C}$ (°)
10	Cl02/A	108 Ala′/A	3.6	175.4	83.4
10	Cl02/B	108 Ala′/B	3.6	174.9	87.8
11	Cl01/A	108 Ala′/A	3.7	173.4	85.1
11	Cl01/B	108 Ala′/B	3.7	175.3	84.3
Average			3.7	174.8	85.2

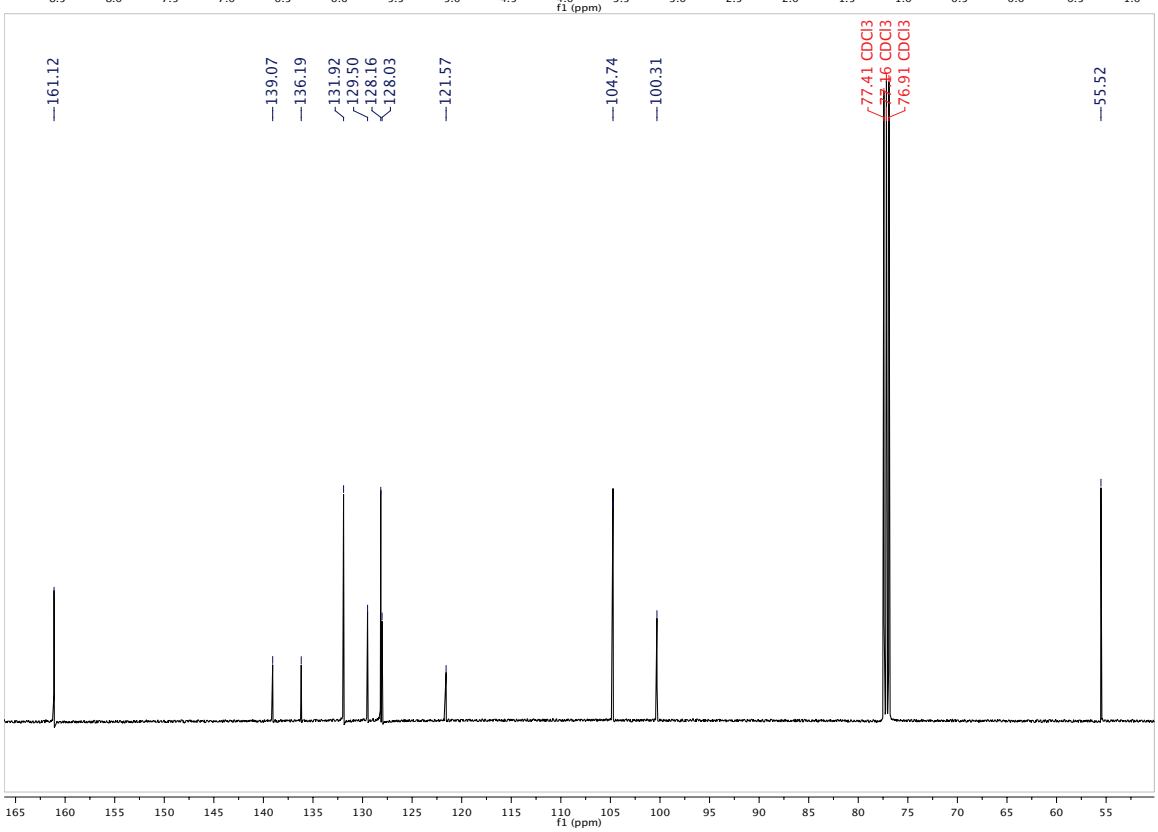
HPLC Traces


Compound 2
Compound 3
Compound 5
Abittrary Units
2.414
3.235
2.713
time (min)
time (min)
time (min)

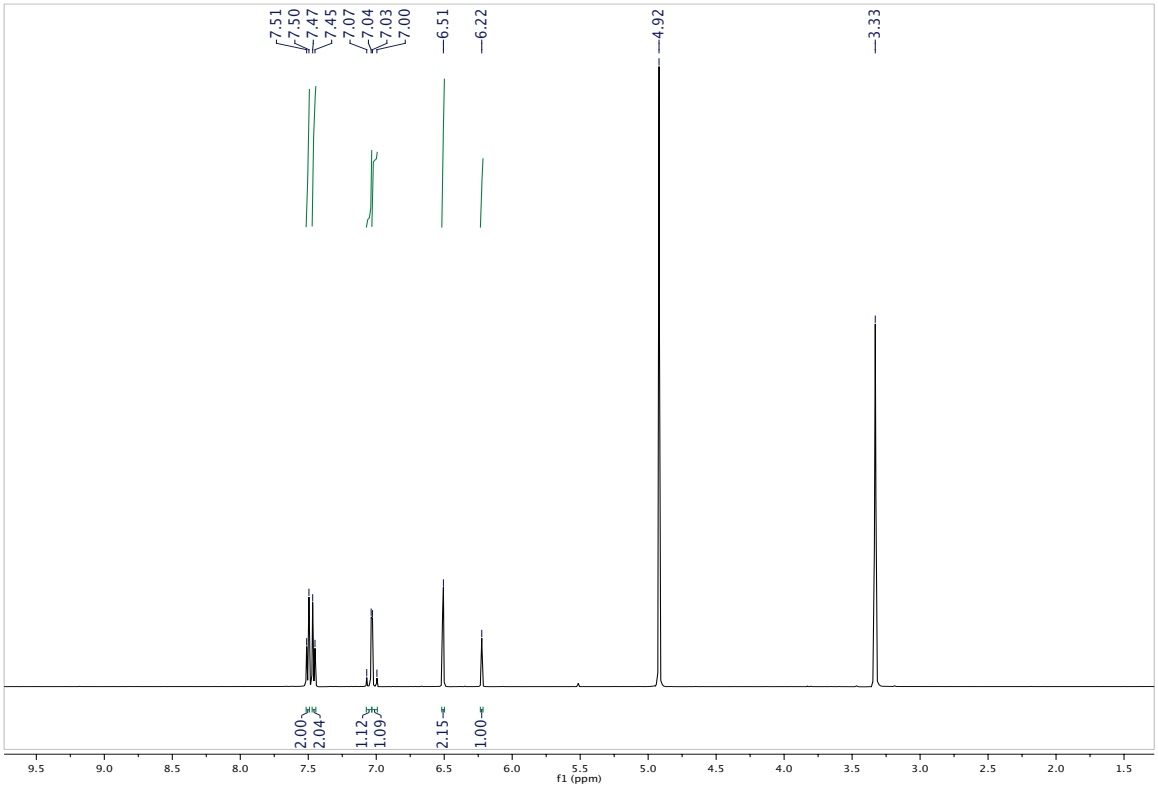
NMR Spectra

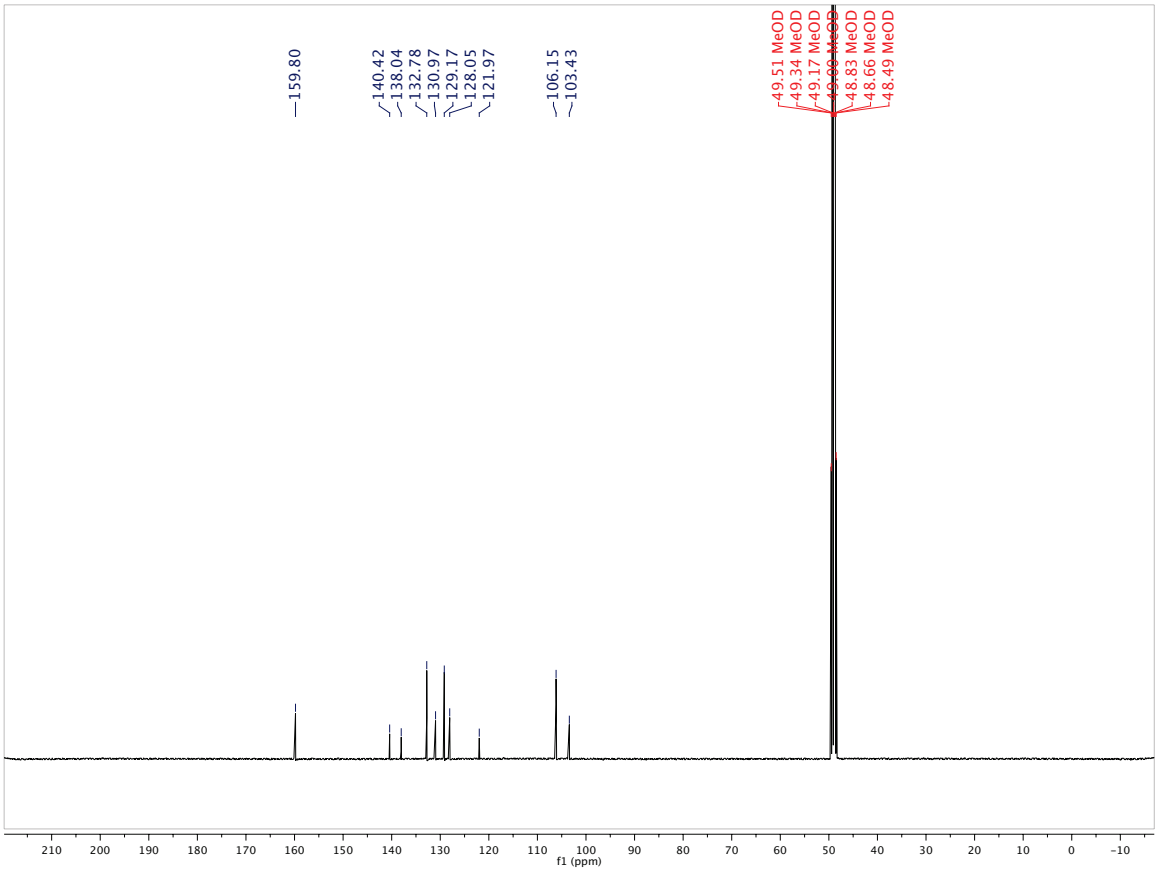
^{1}H NMR ($CDCl_3$) and ^{13}C NMR ($CDCl_3$) of Compound **2a**



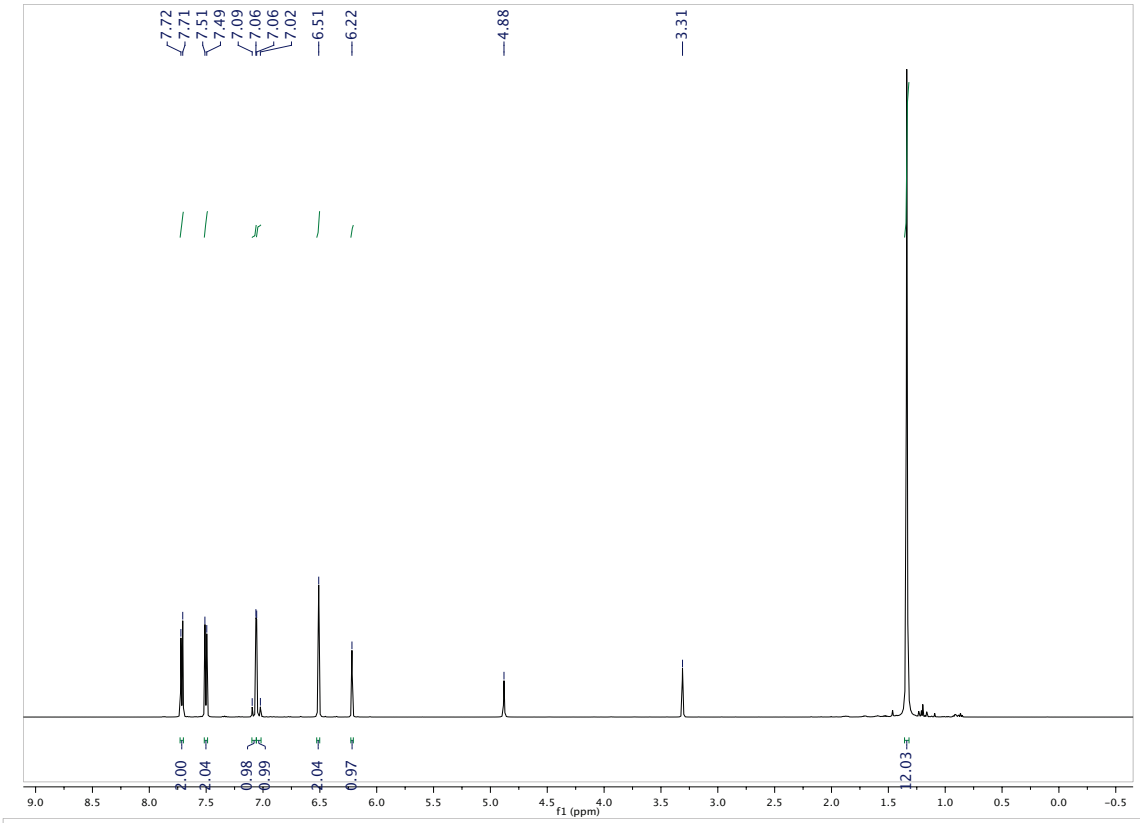


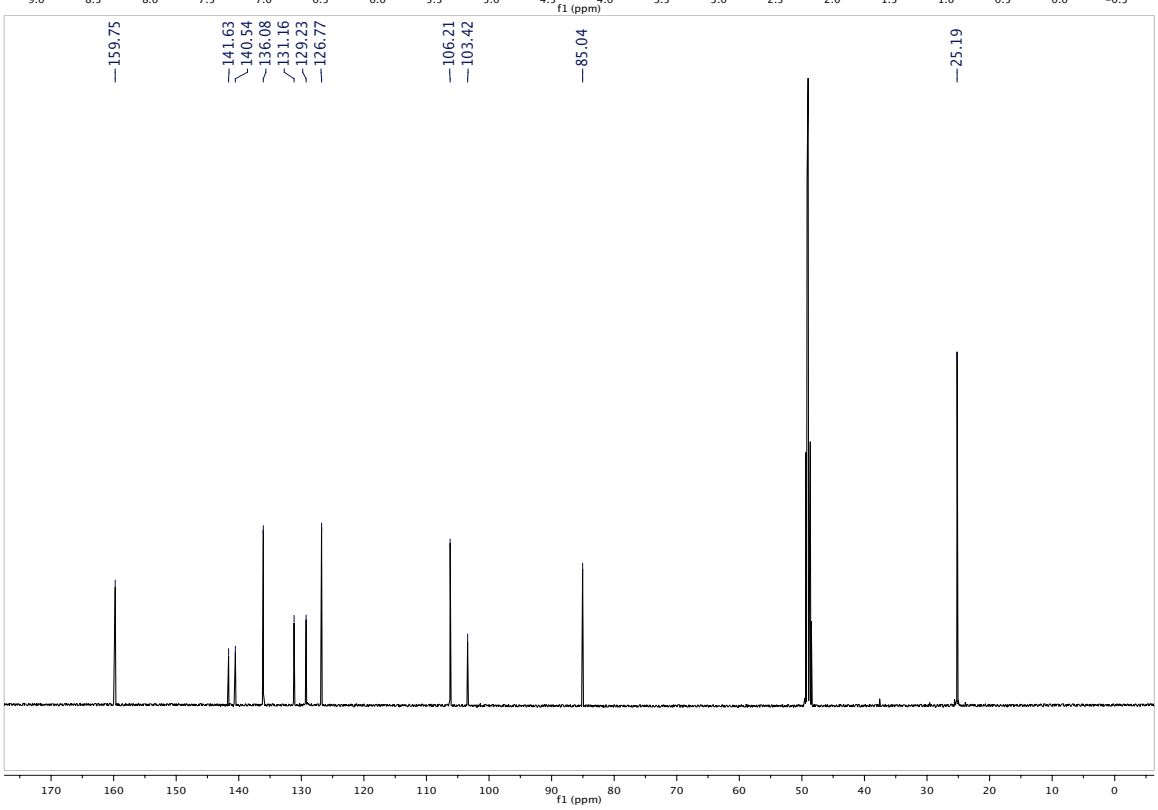
^{1}H NMR (CD_3OD) and ^{13}C NMR (CD_3OD) of Compound **2b**



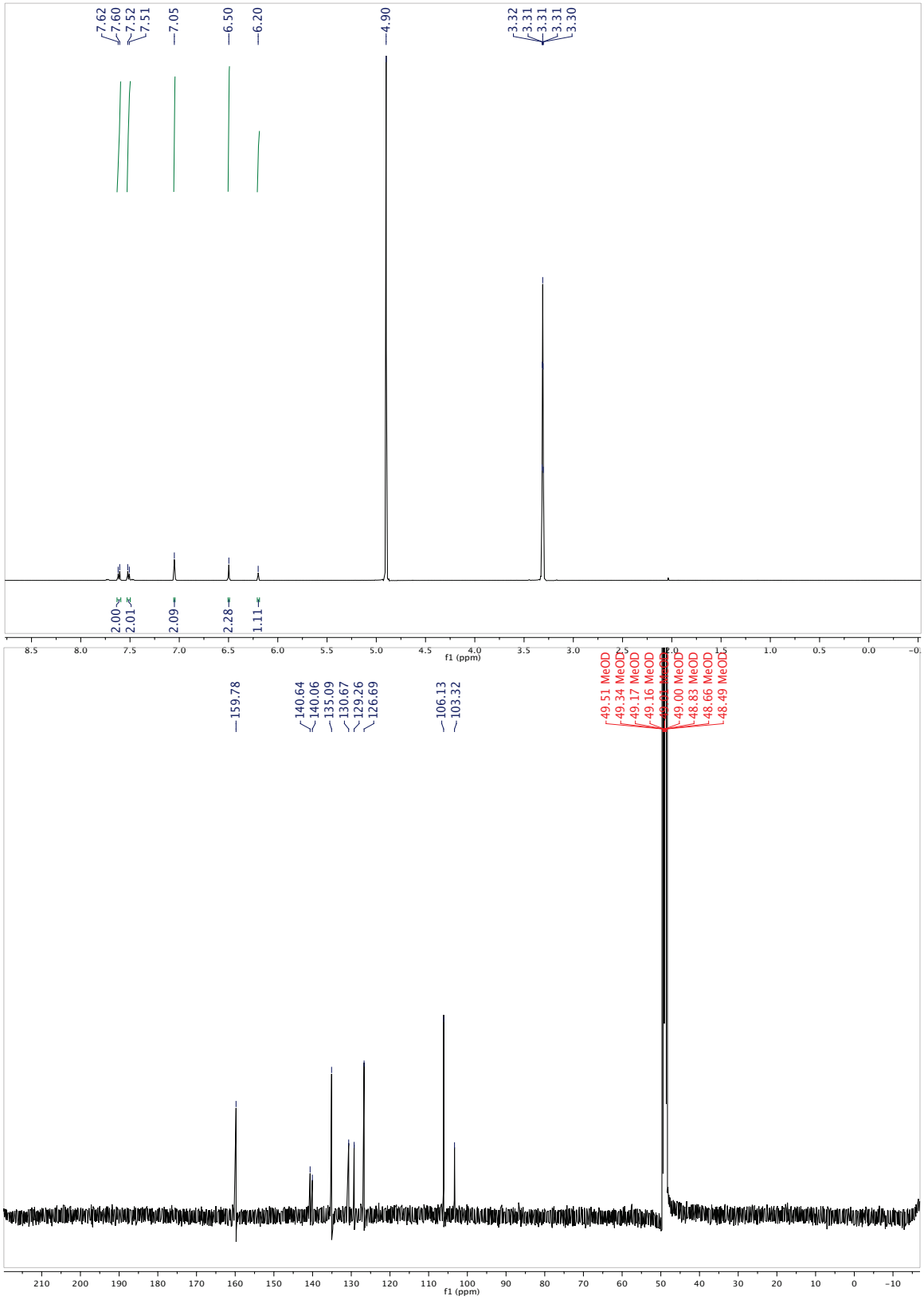


^{1}H NMR (CD_3OD) and ^{13}C NMR (CD_3OD) of Compound **2c**

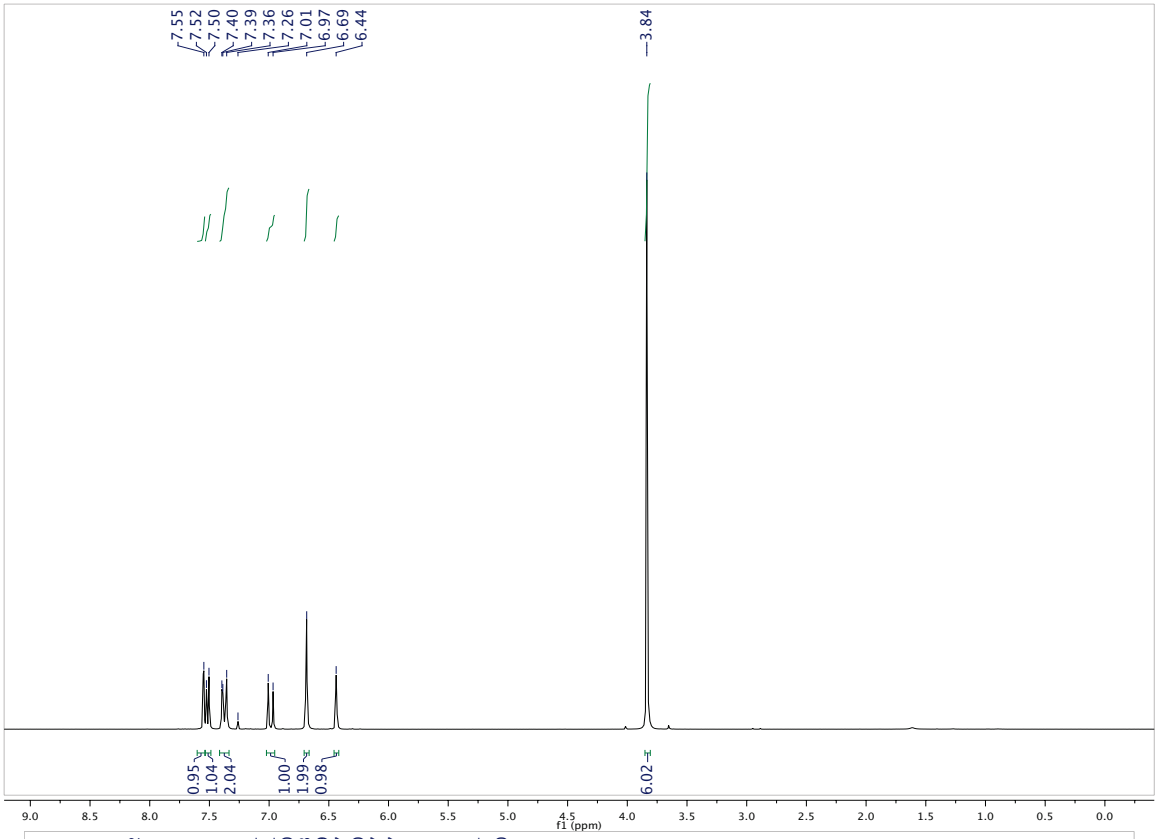


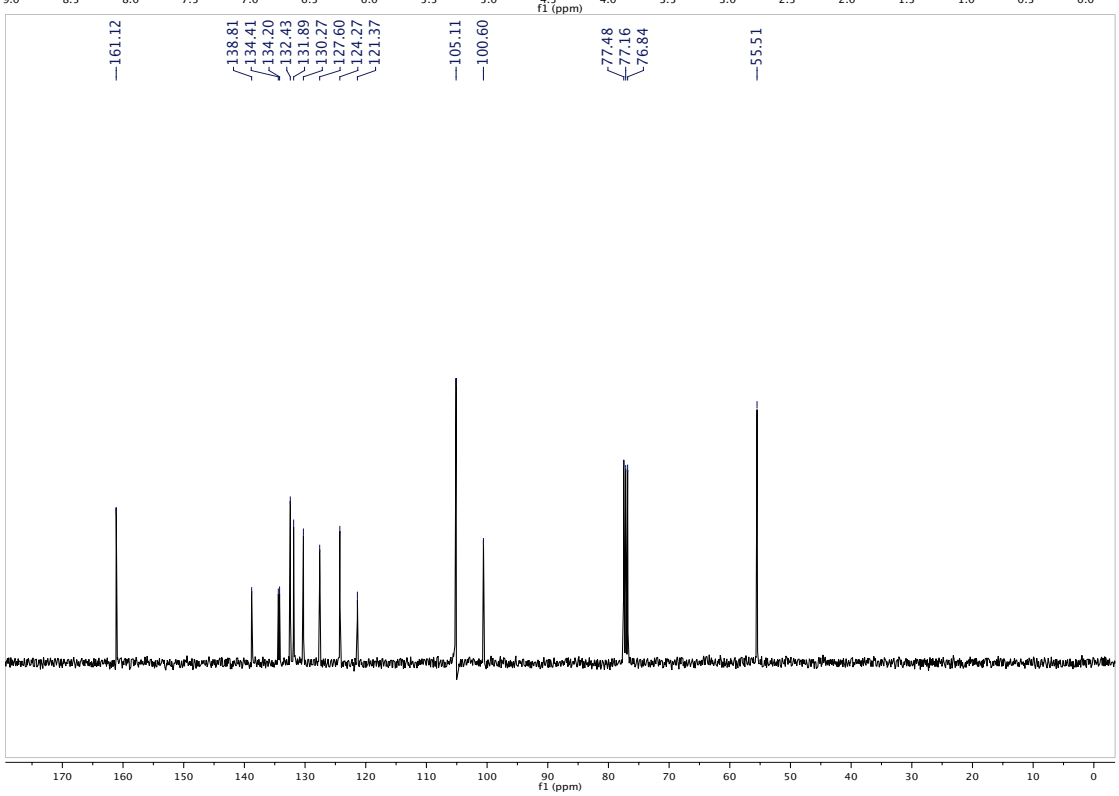


^{1}H NMR (CD_3OD) and ^{13}C NMR (CD_3OD) of Compound **2**

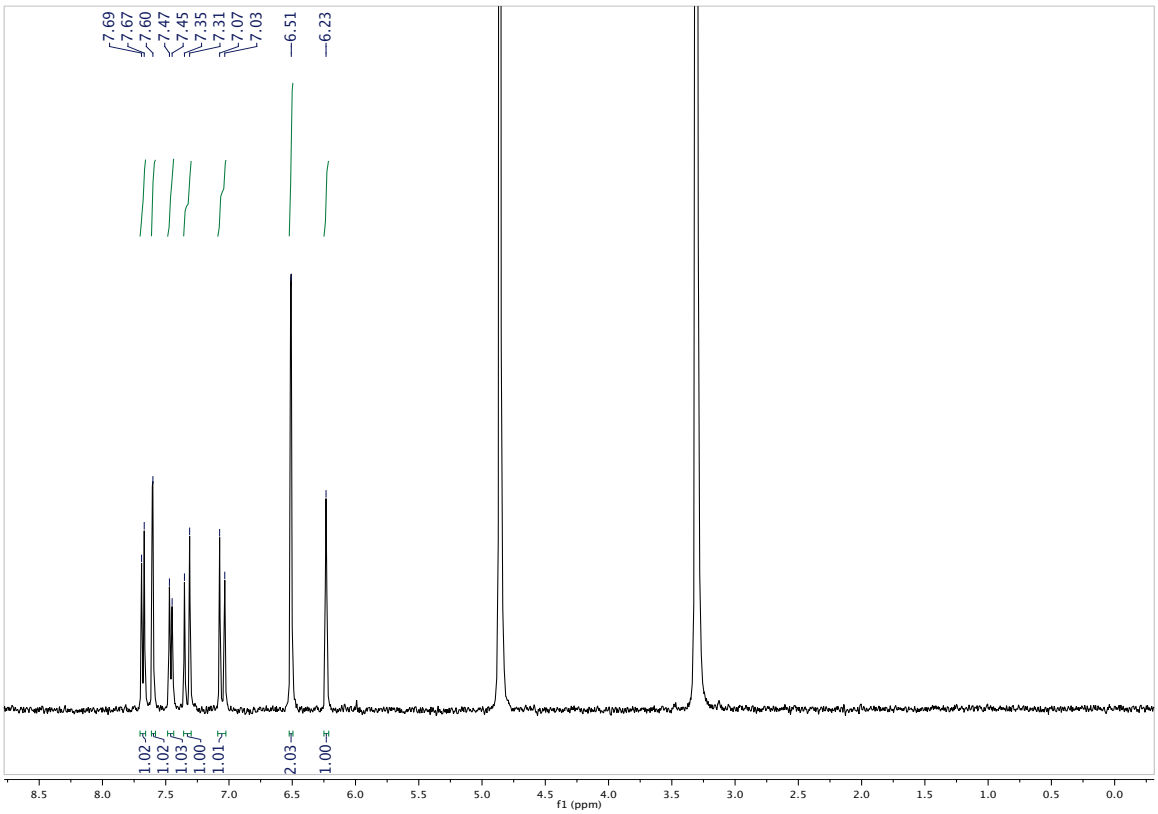


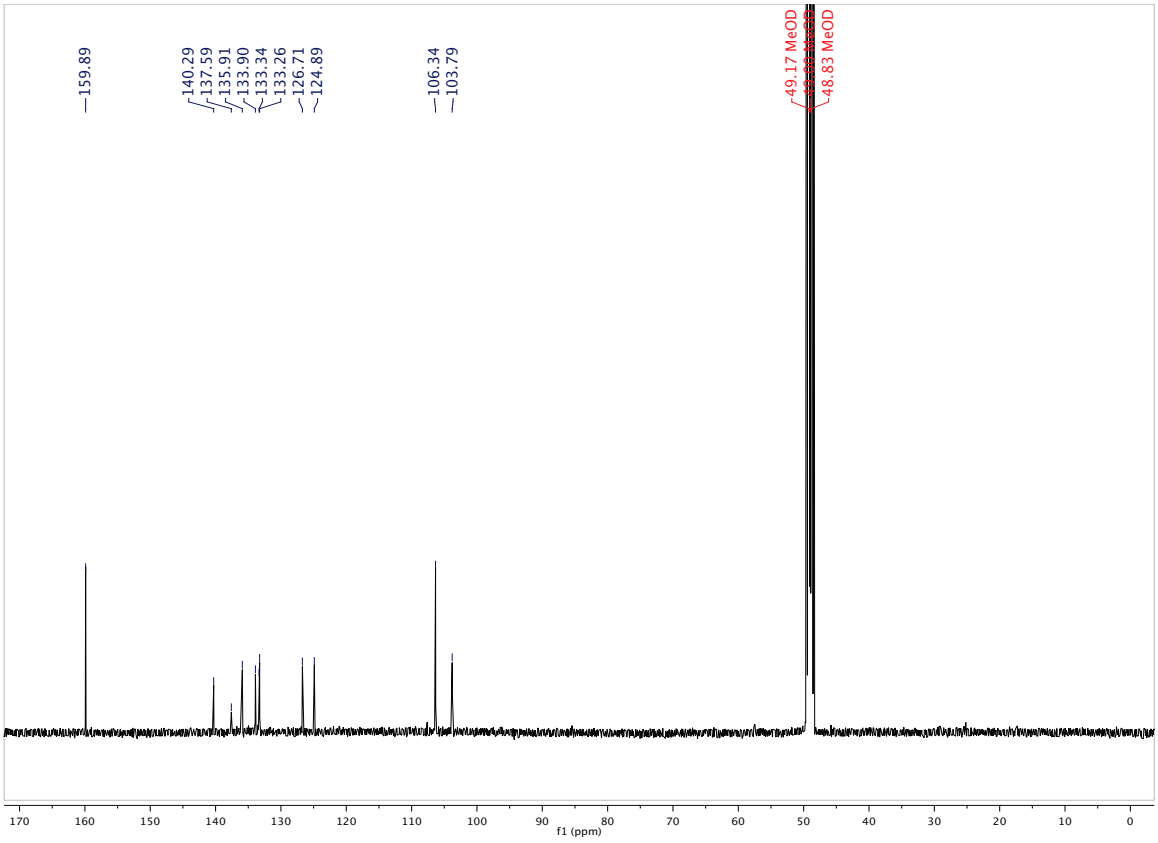
^{1}H NMR ($CDCl_3$) and ^{13}C NMR ($CDCl_3$) of Compound **3a**



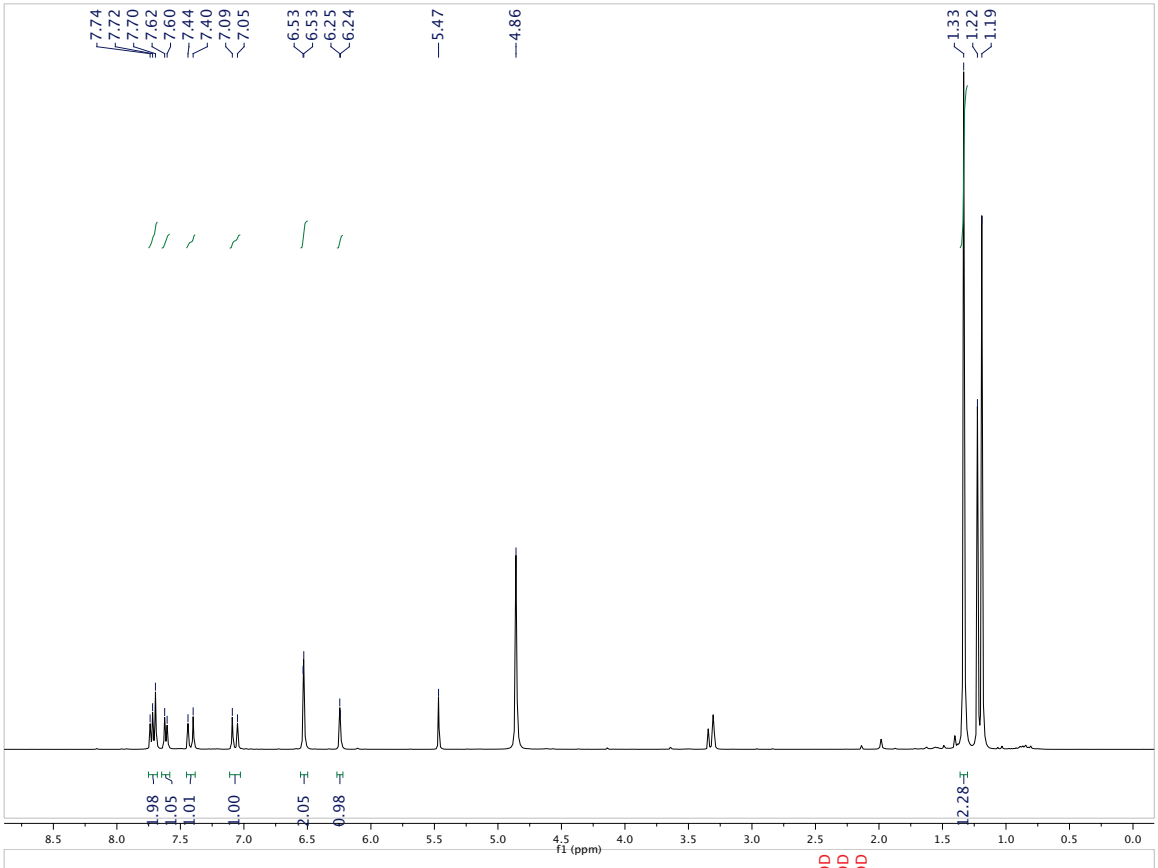


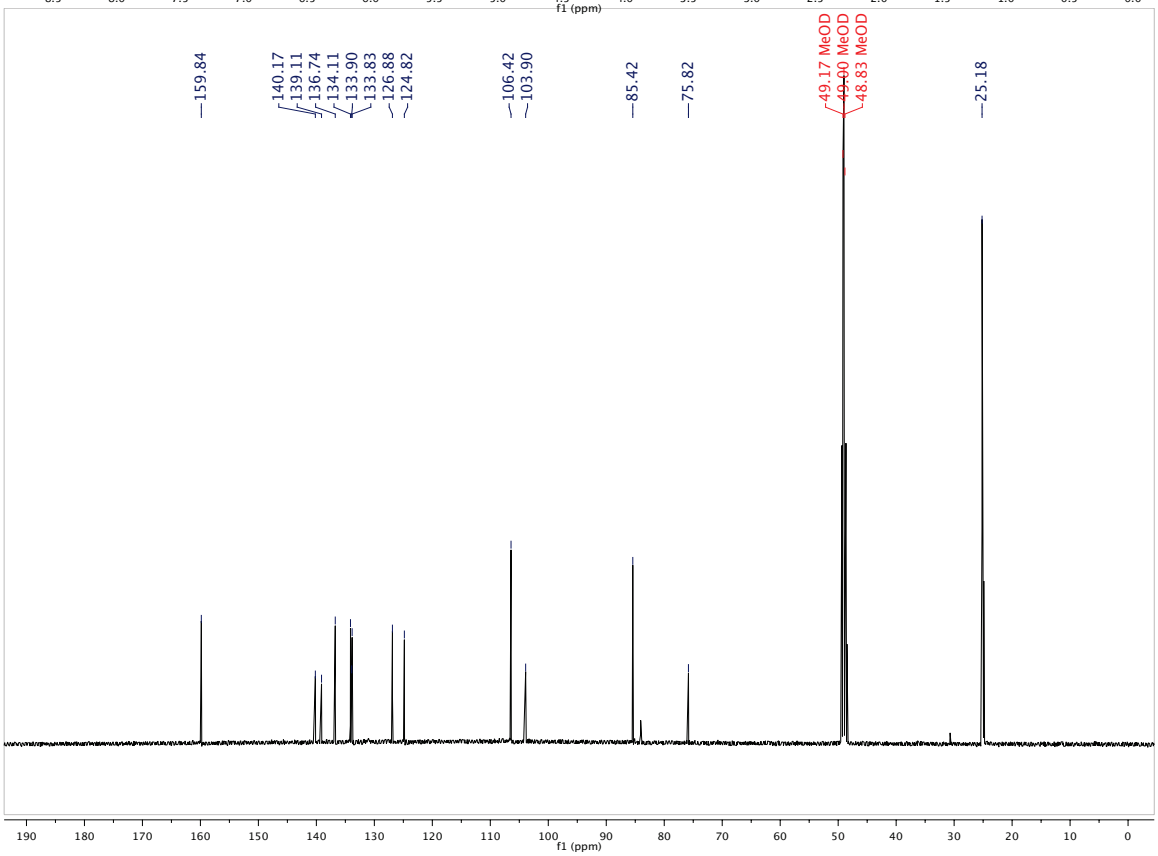
^{1}H NMR (CD_3OD) and ^{13}C NMR (CD_3OD) of Compound **3b**



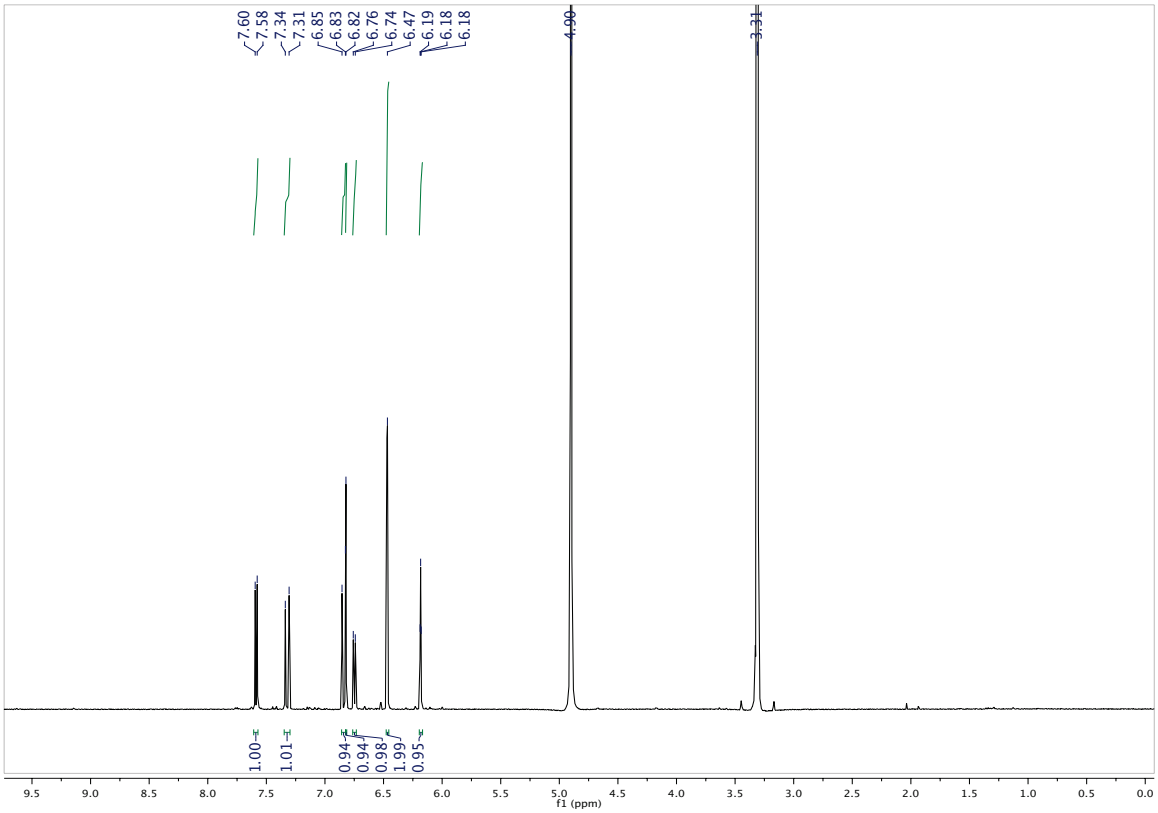


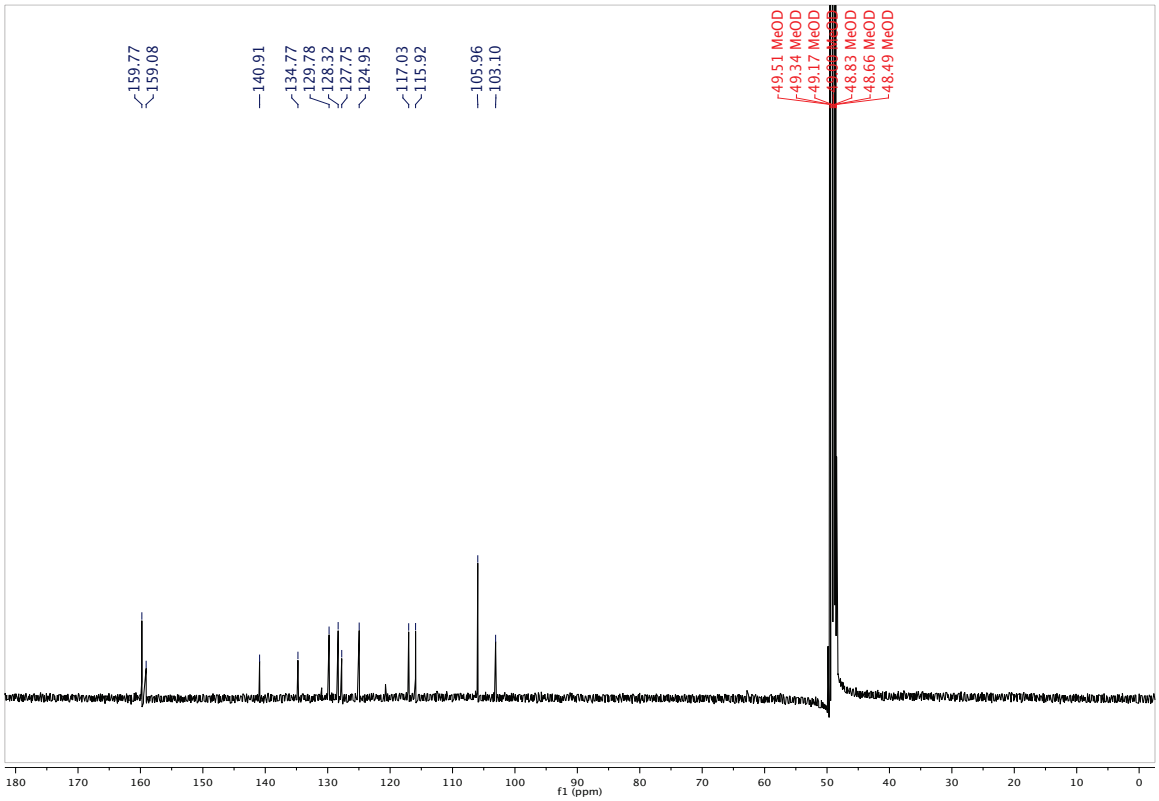
^{1}H NMR (CD_3OD) and ^{13}C NMR (CD_3OD) of Compound **3c**



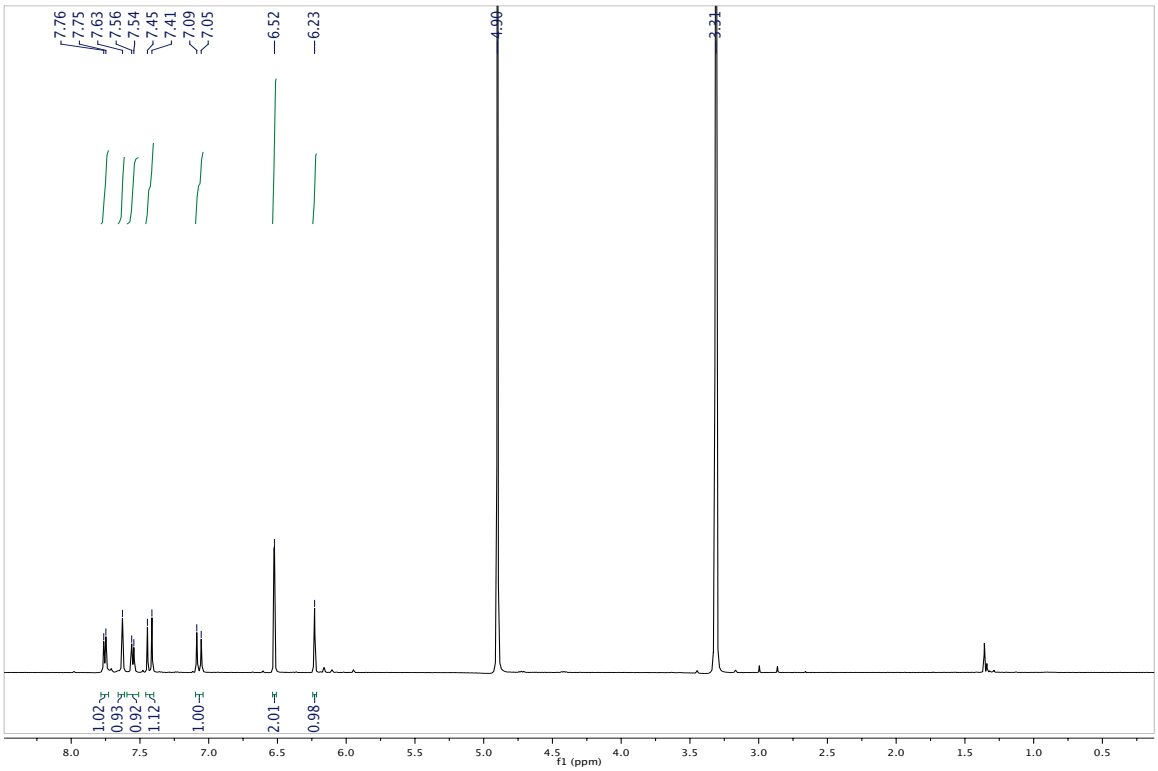


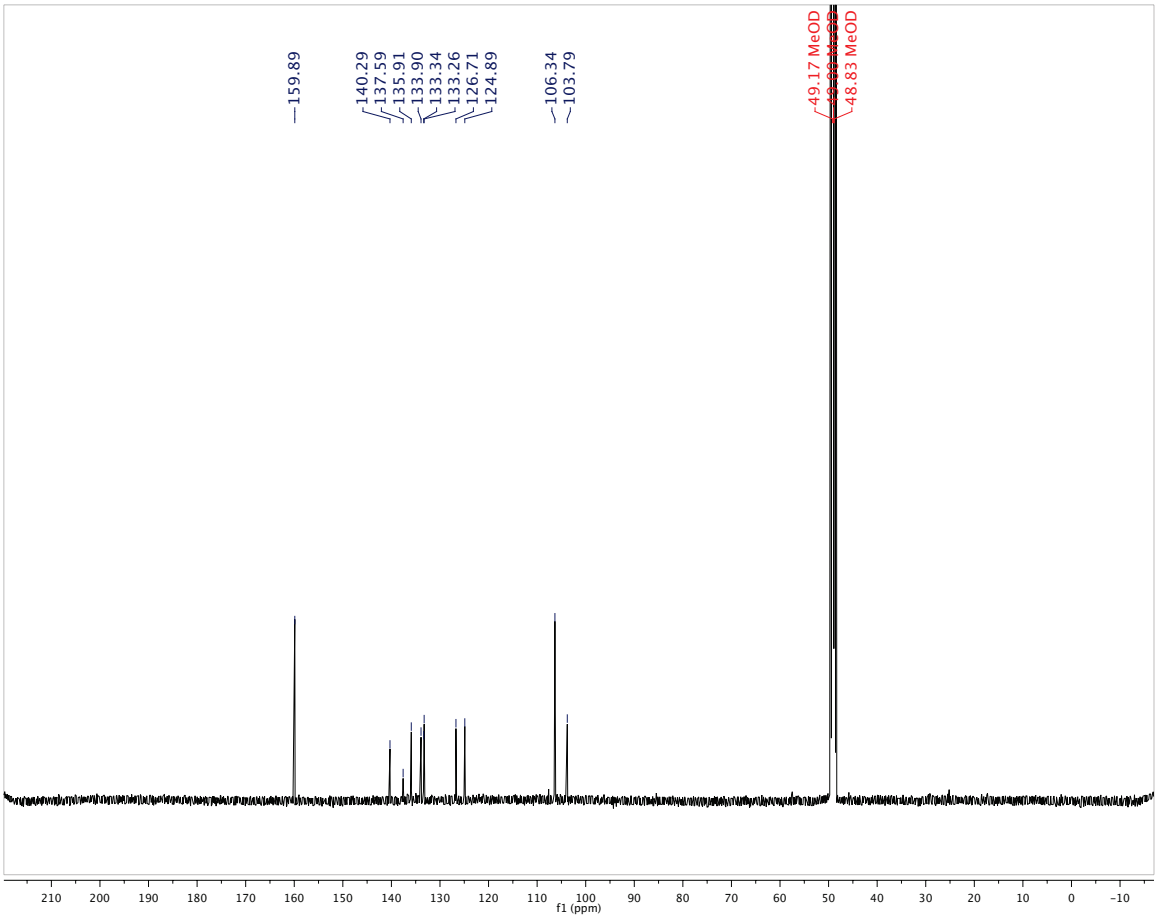
^{1}H NMR (CD_3OD) and ^{13}C NMR (CD_3OD) of Compound **3**



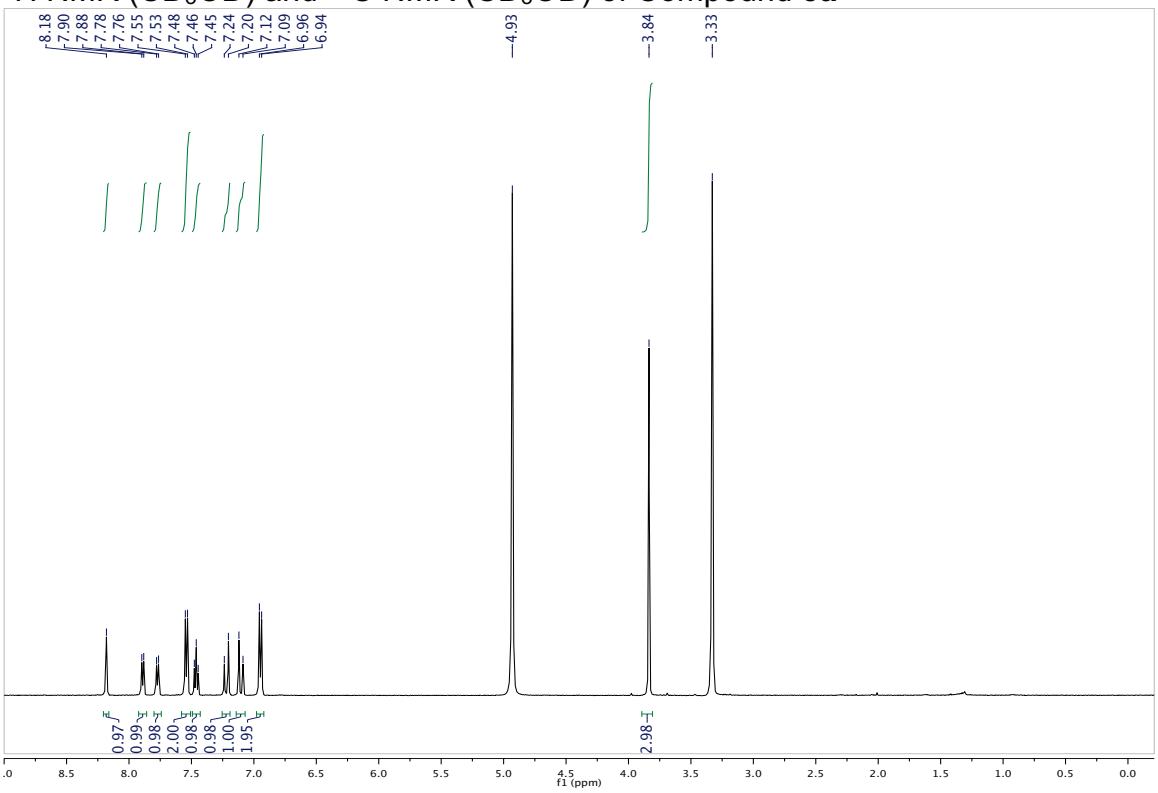


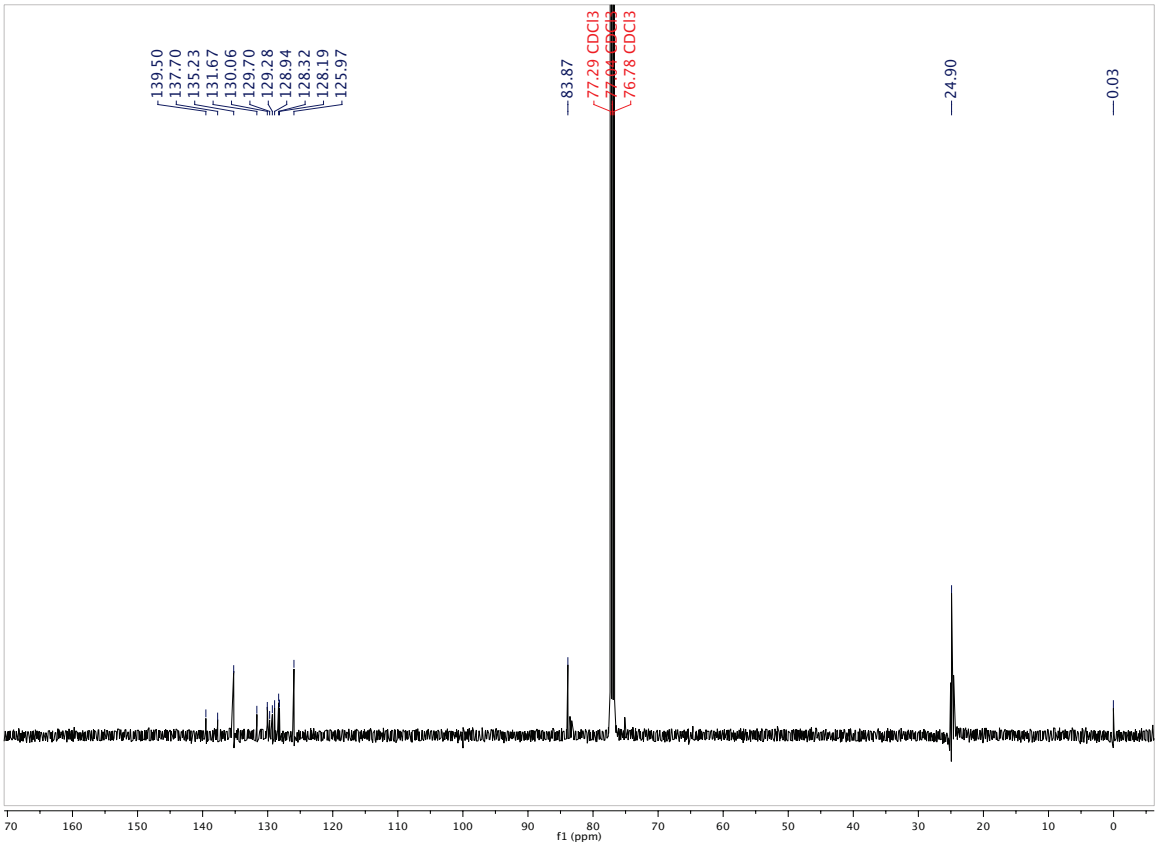
^{1}H NMR (CD_3OD) and ^{13}C NMR (CD_3OD) of Compound **4**



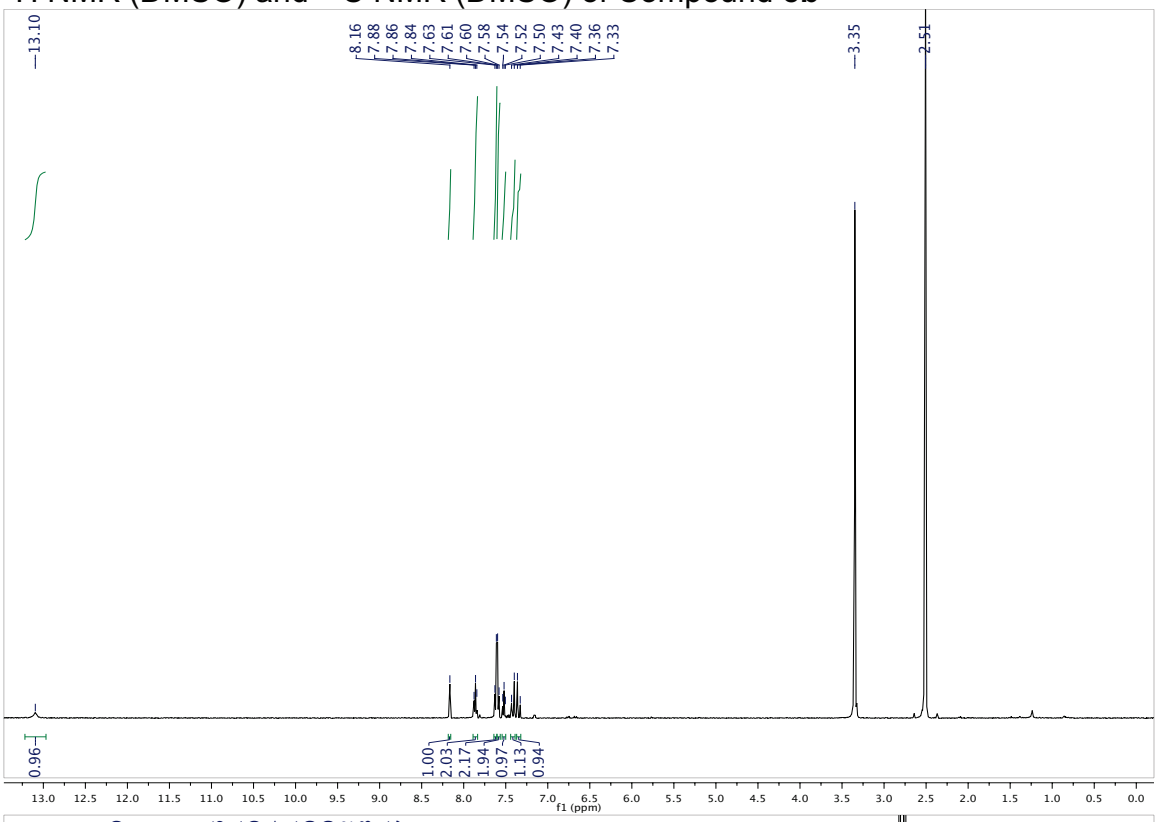


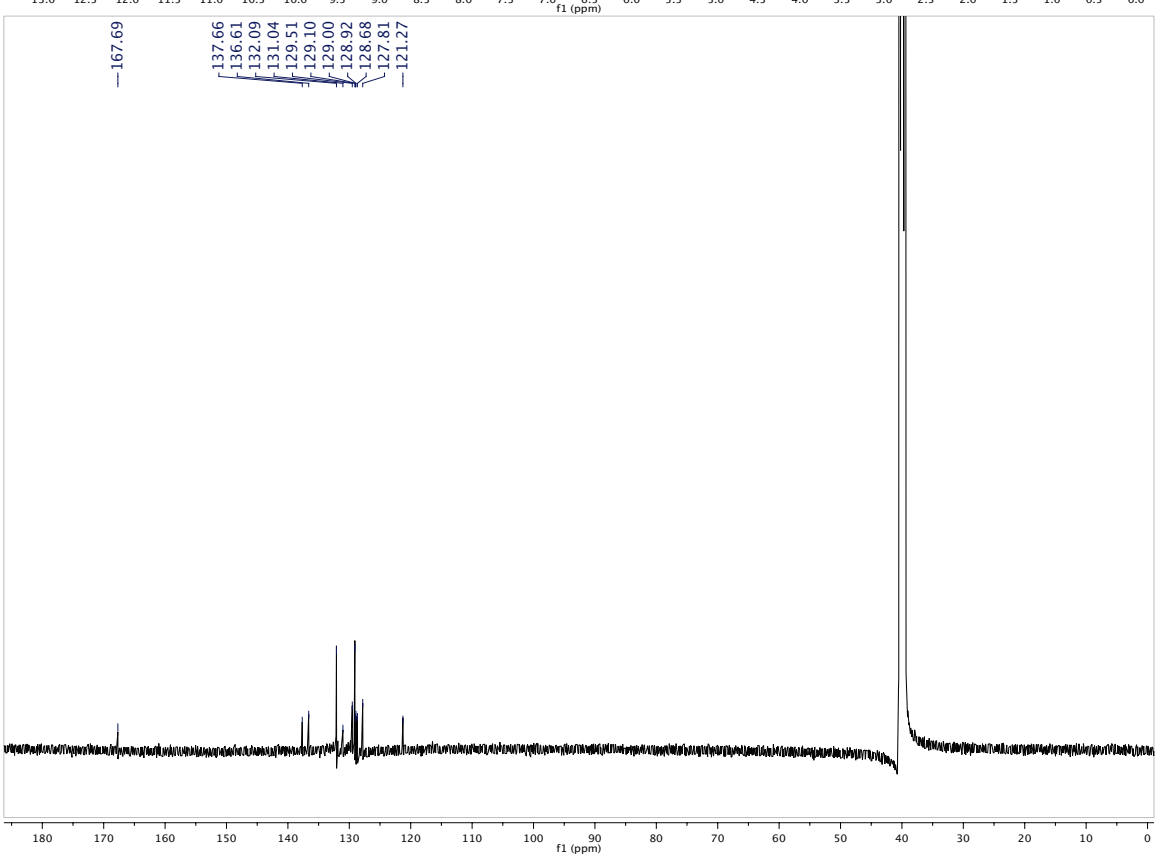
^{1}H NMR (CD_3OD) and ^{13}C NMR (CD_3OD) of Compound **5a**



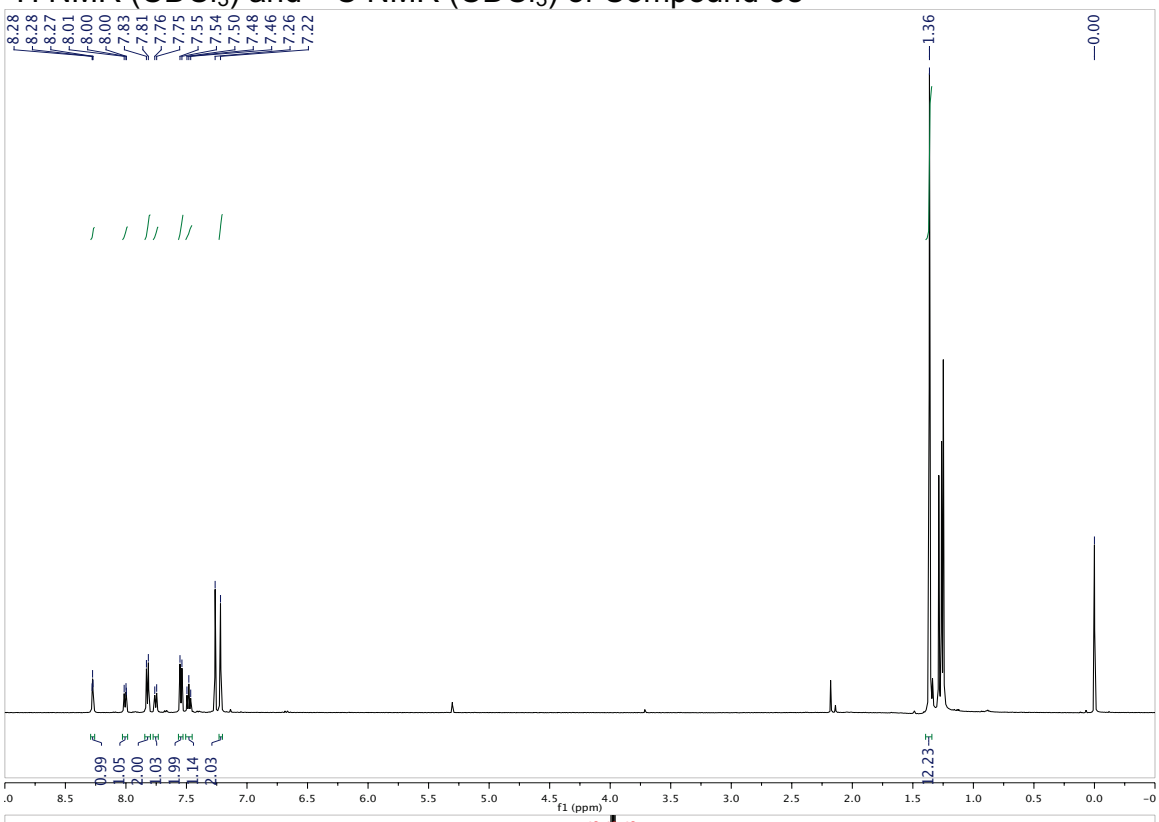


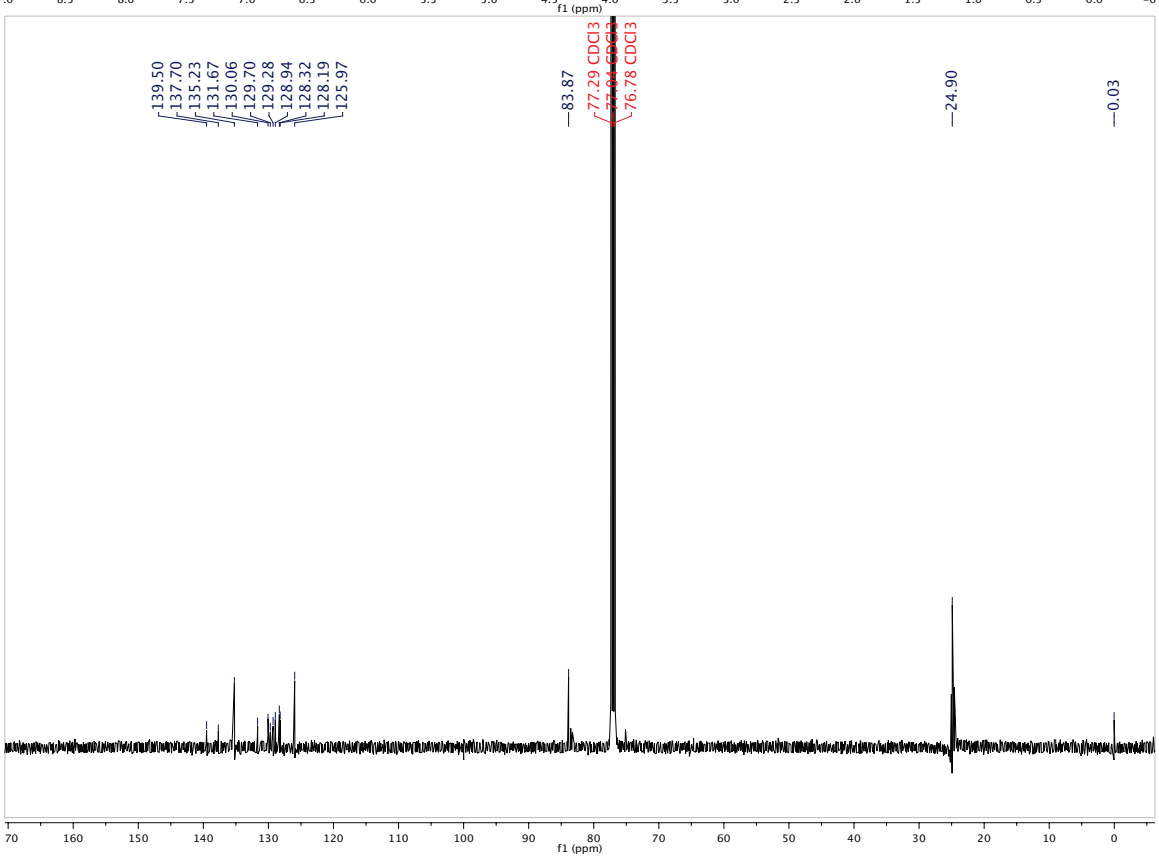
^{1}H NMR (DMSO) and ^{13}C NMR (DMSO) of Compound **5b**



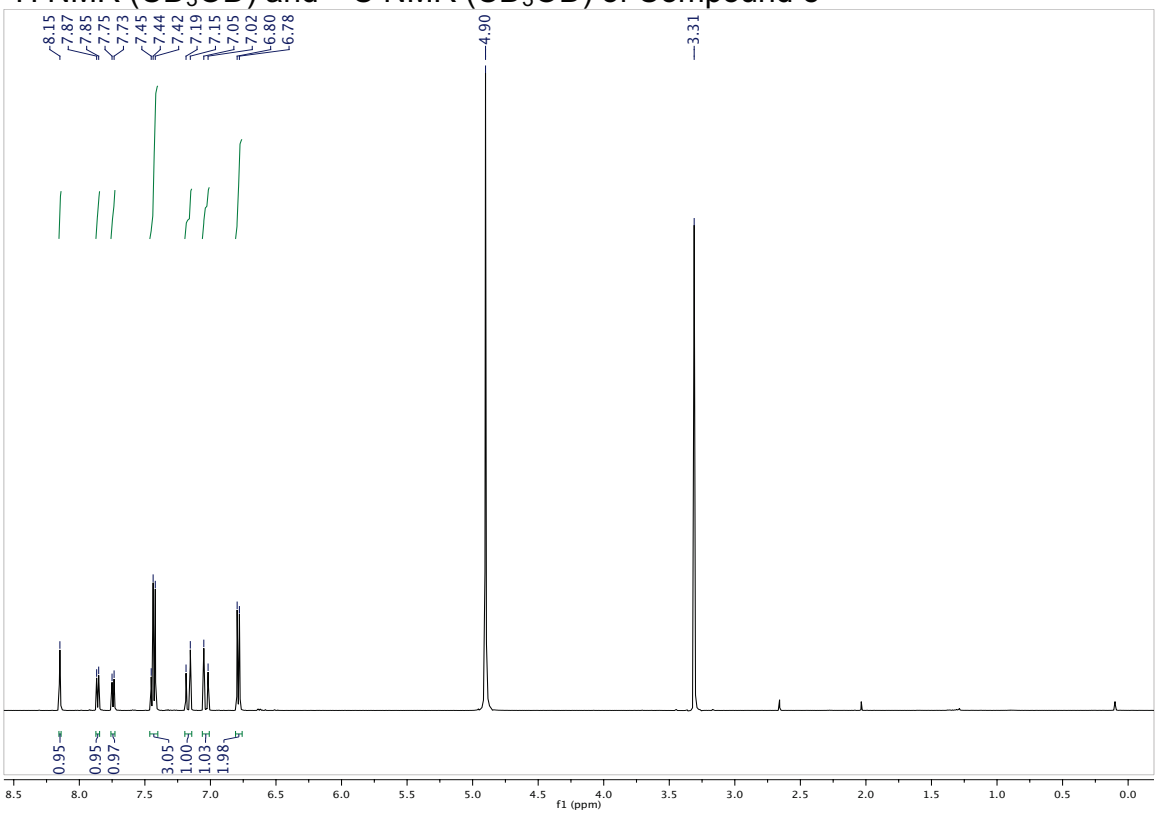


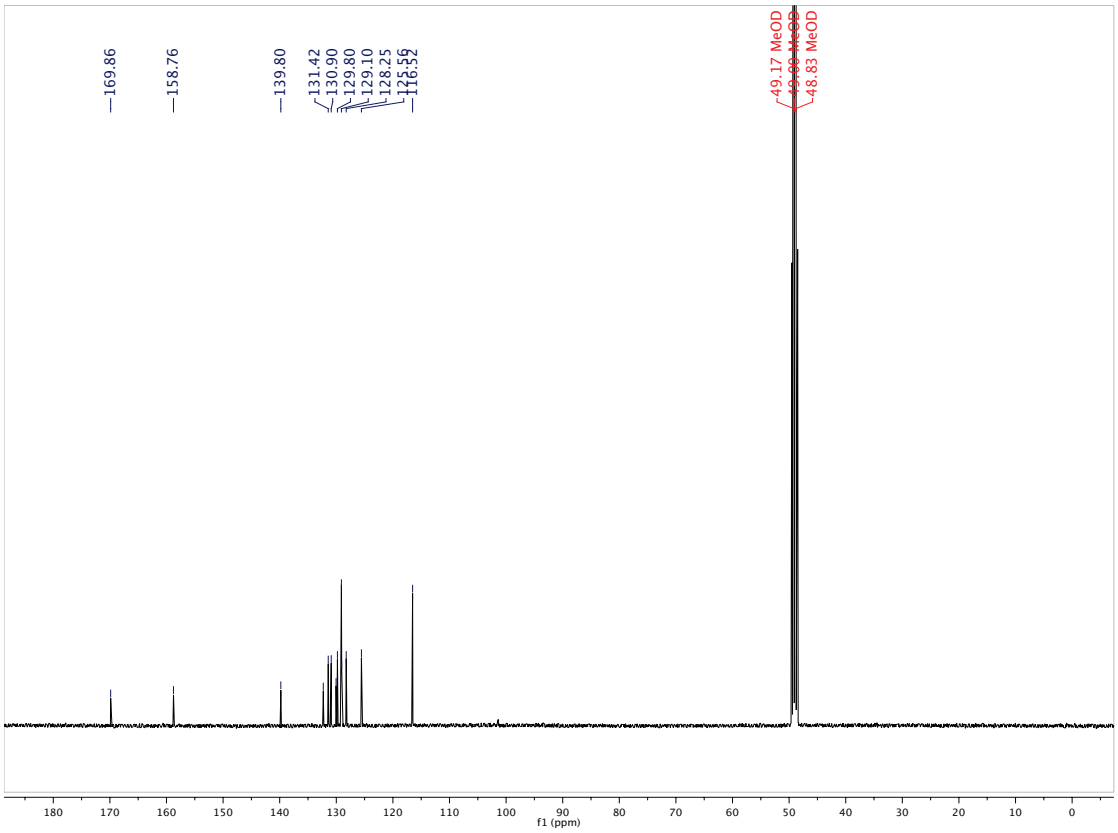
^{1}H NMR ($CDCl_3$) and ^{13}C NMR ($CDCl_3$) of Compound **5c**



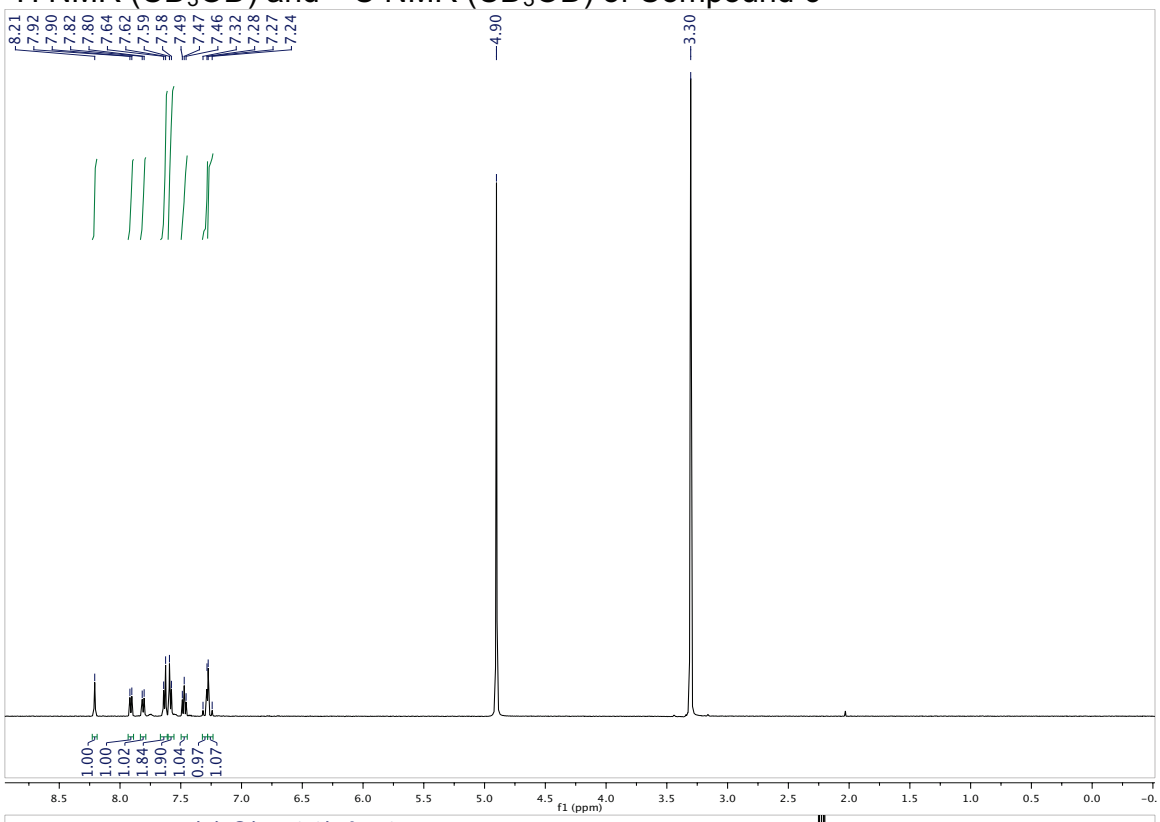


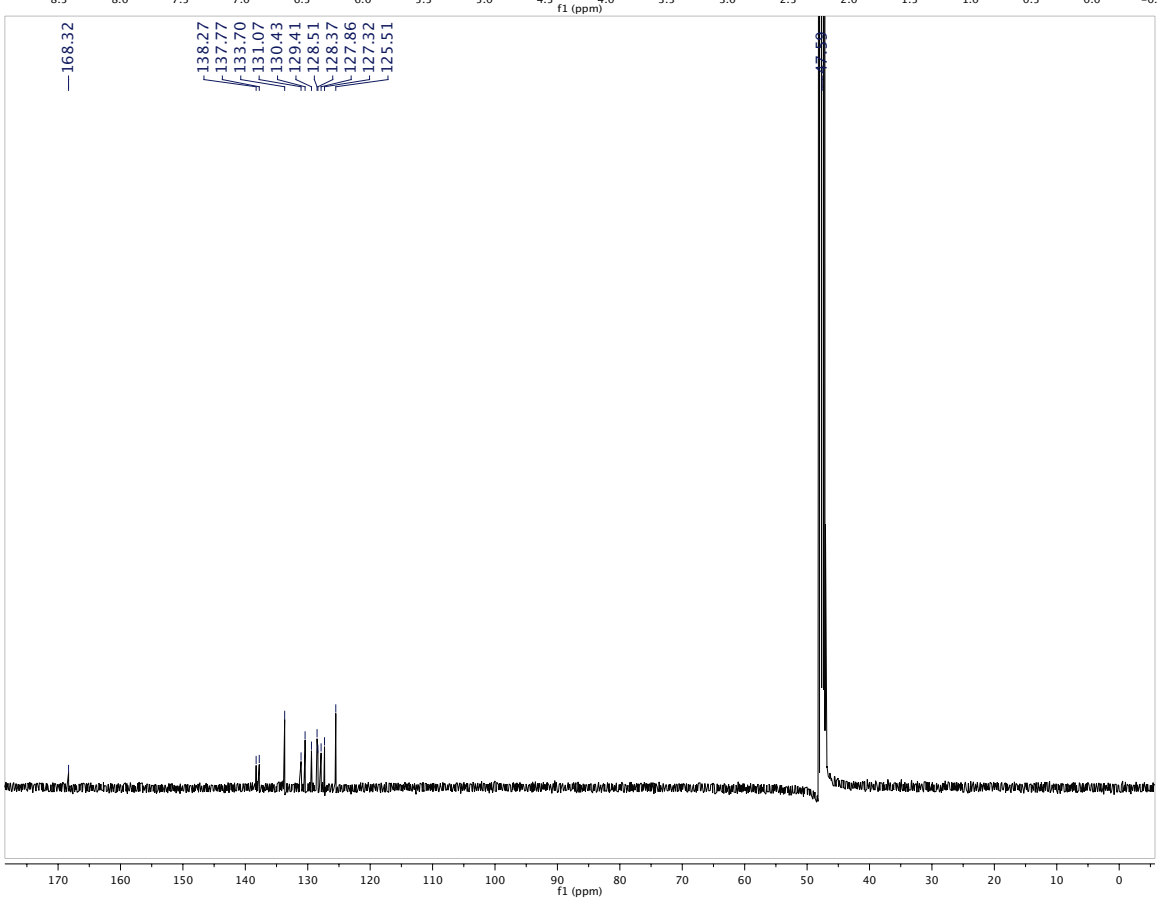
^{1}H NMR (CD_3OD) and ^{13}C NMR (CD_3OD) of Compound **5**



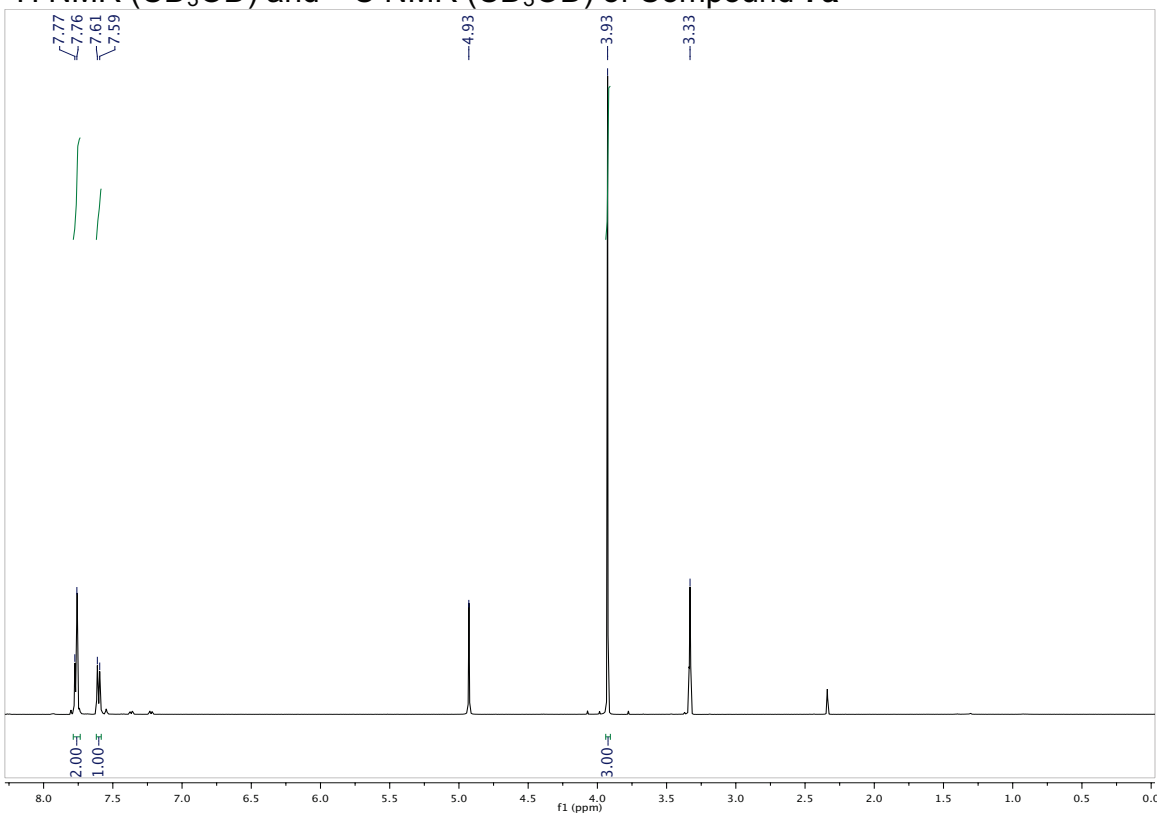


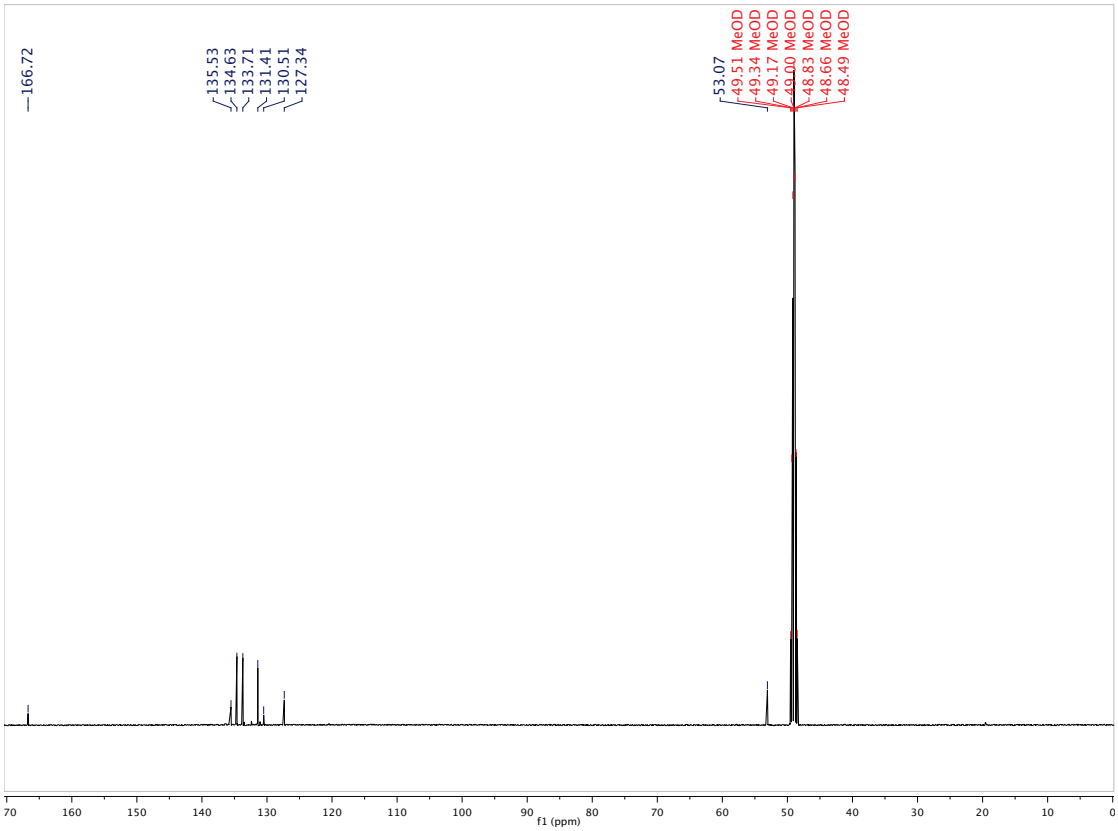
^{1}H NMR (CD_3OD) and ^{13}C NMR (CD_3OD) of Compound **6**



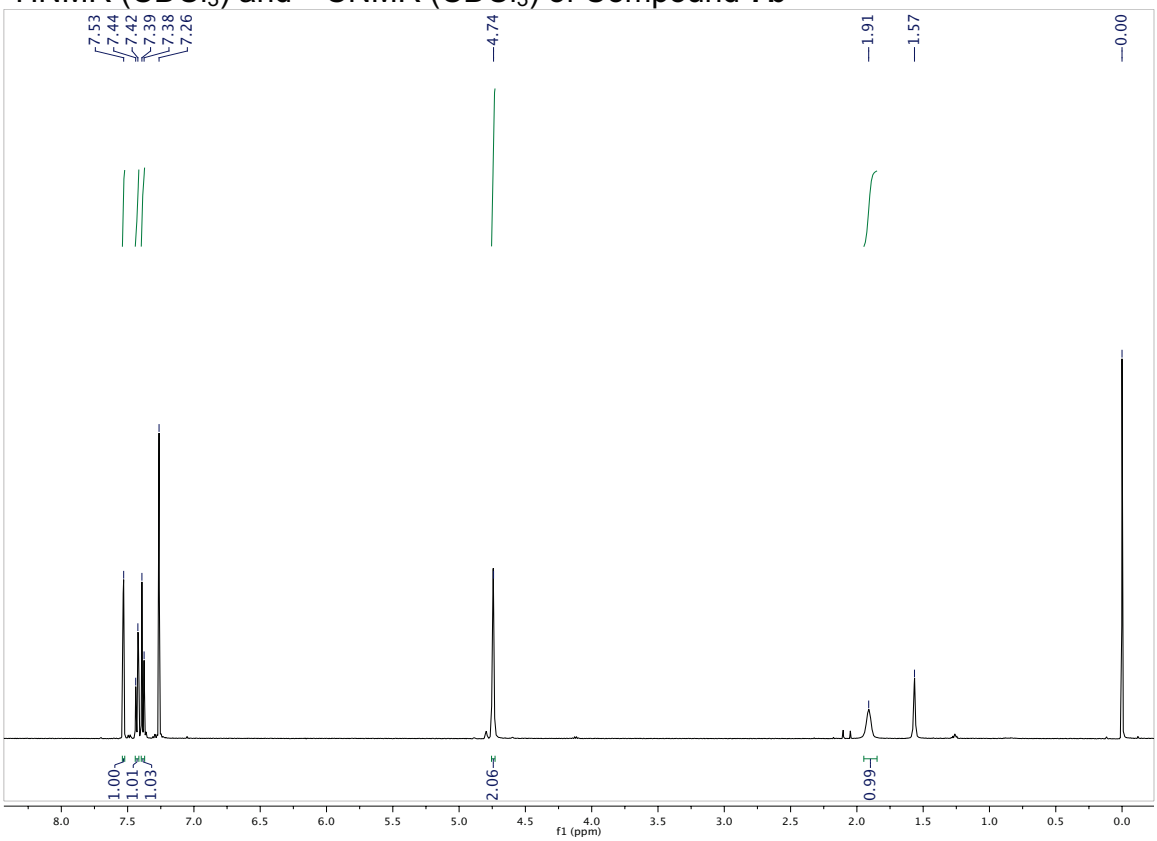


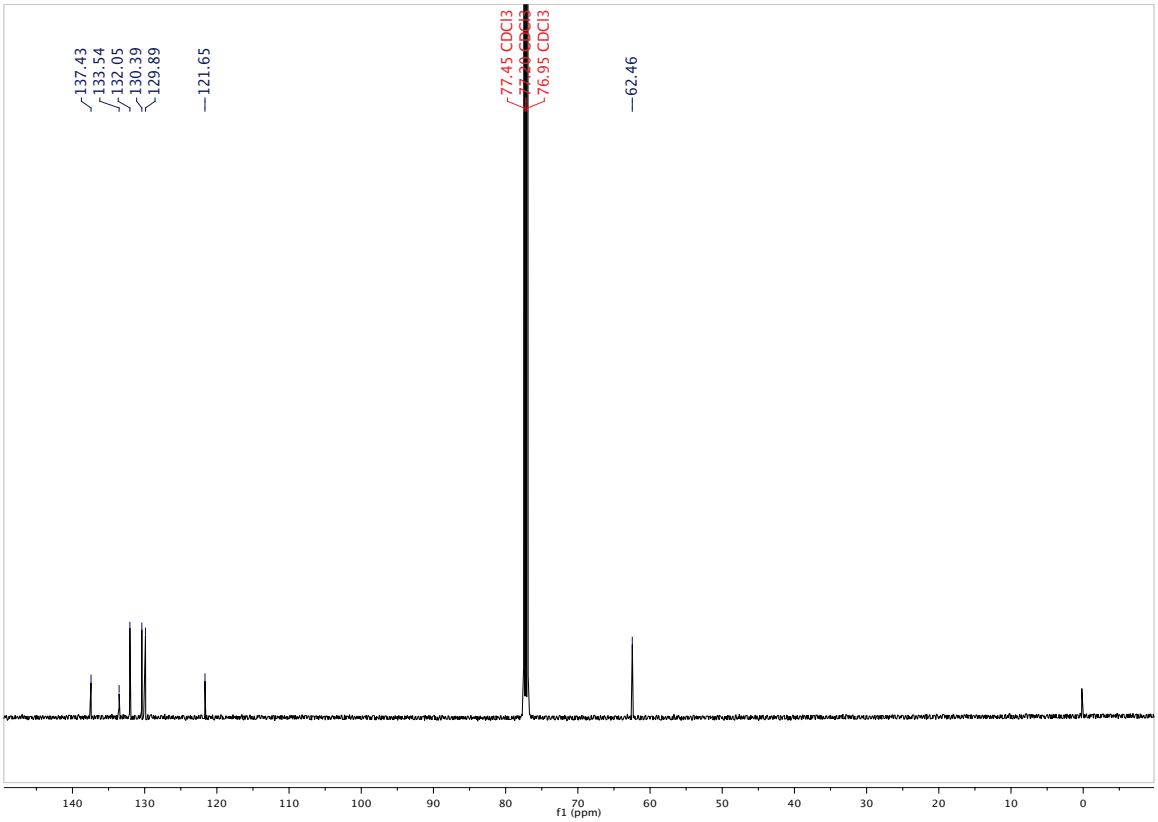
^{1}H NMR (CD_3OD) and ^{13}C NMR (CD_3OD) of Compound **7a**



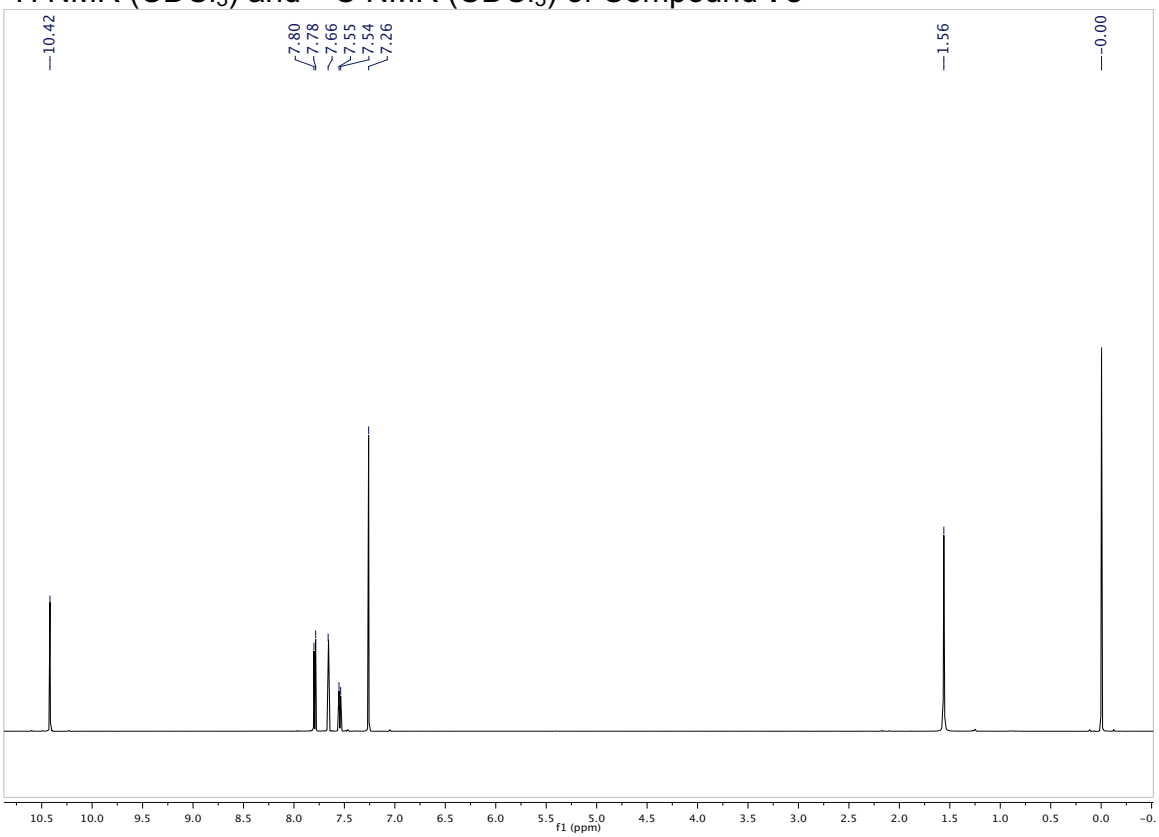


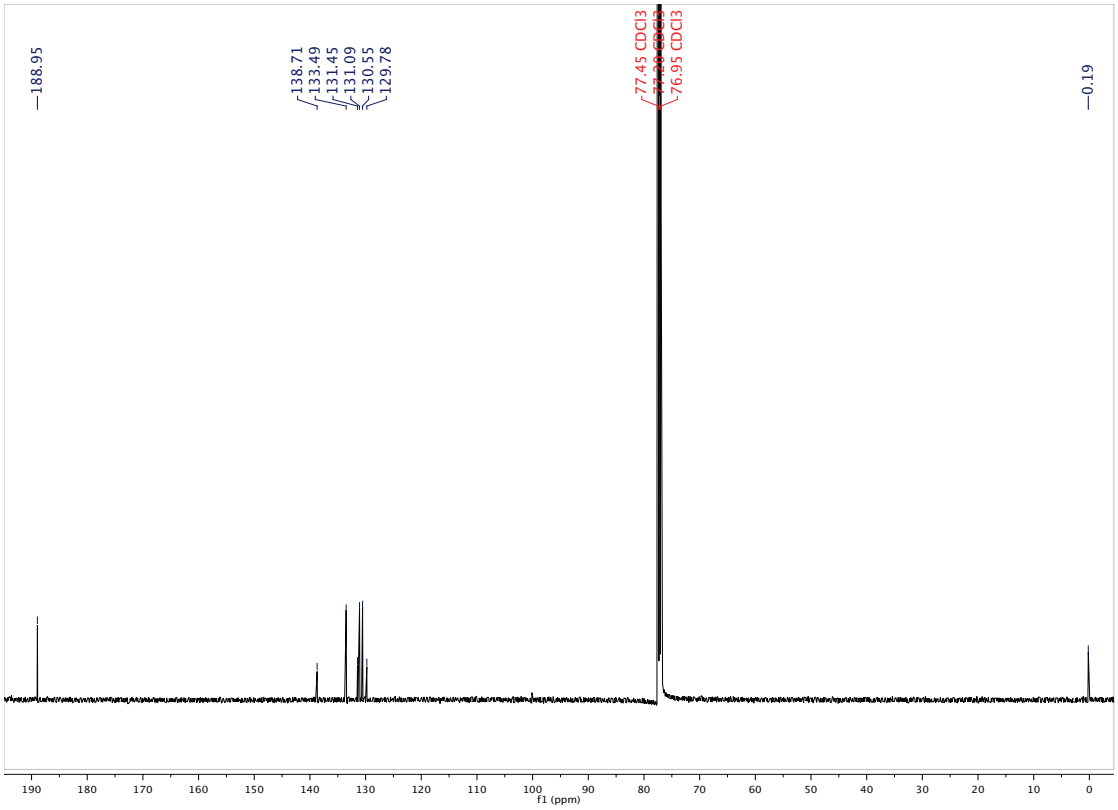
^{1}HNMR ($CDCl_3$) and ^{13}CNMR ($CDCl_3$) of Compound **7b**



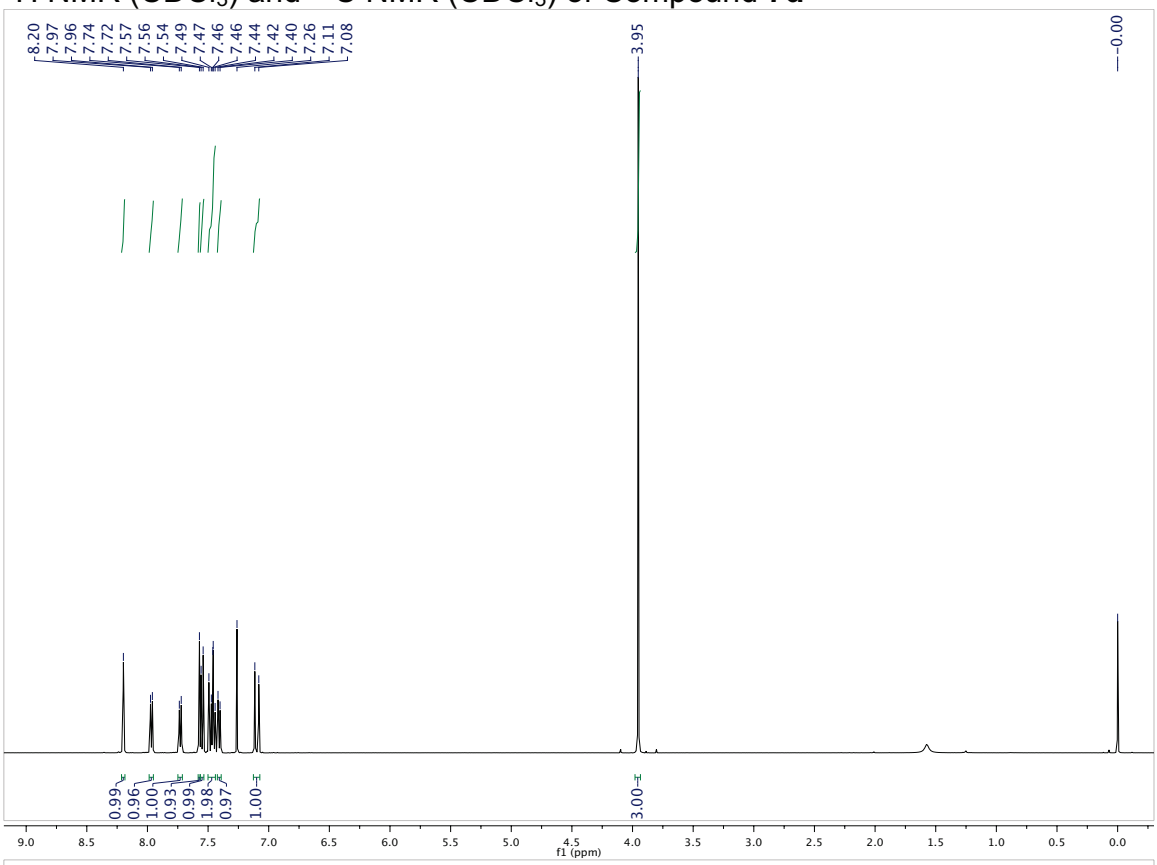


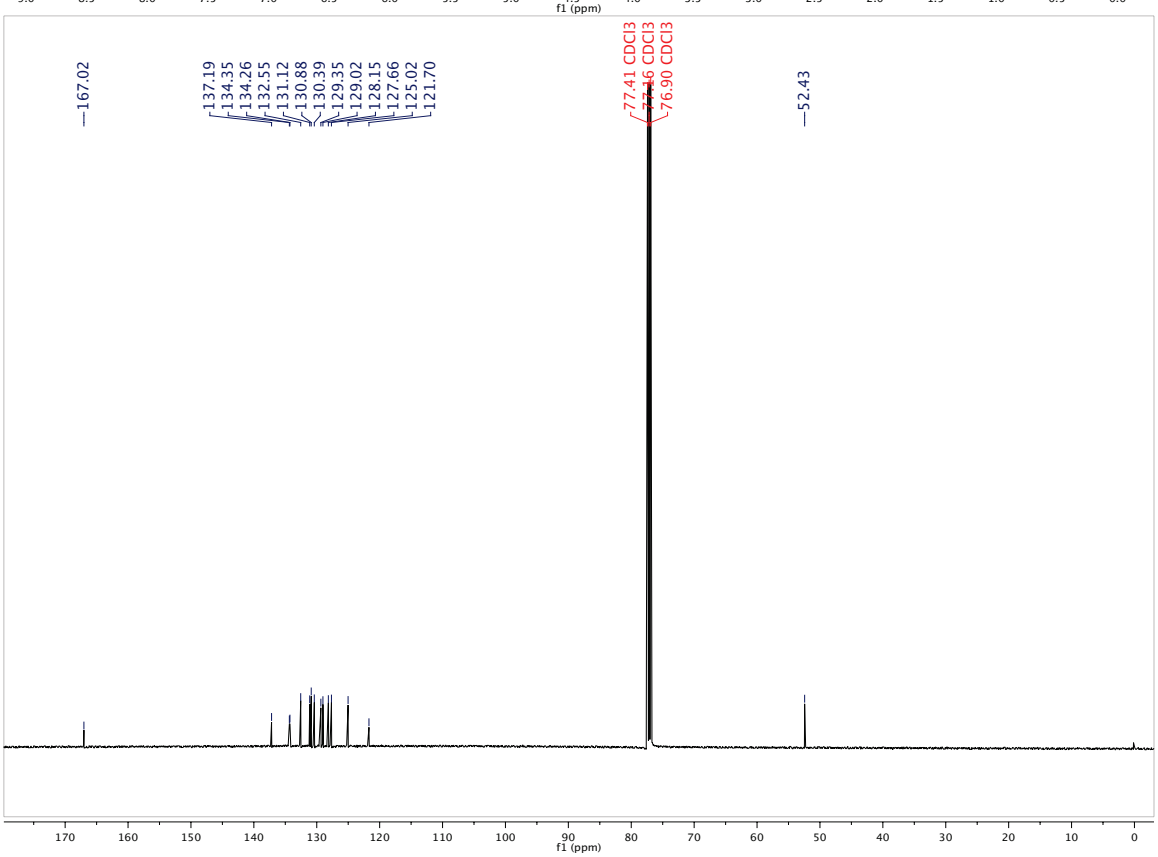
^{1}H NMR ($CDCl_3$) and ^{13}C NMR ($CDCl_3$) of Compound **7c**



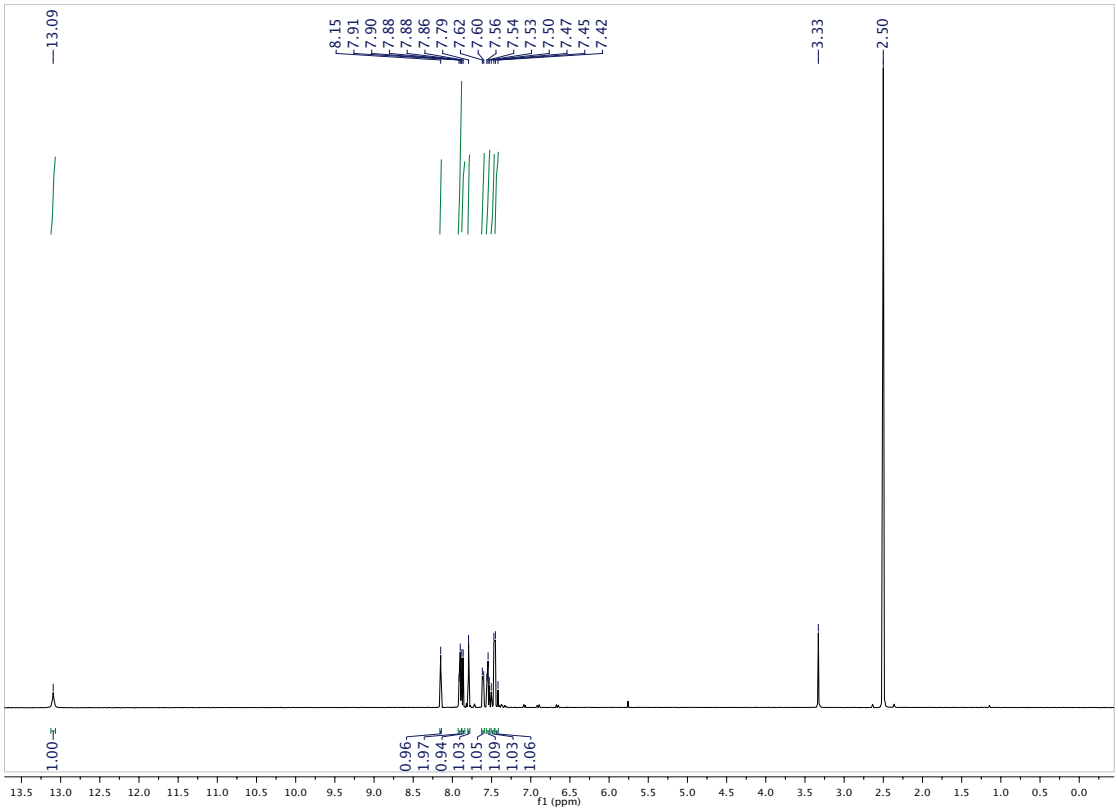


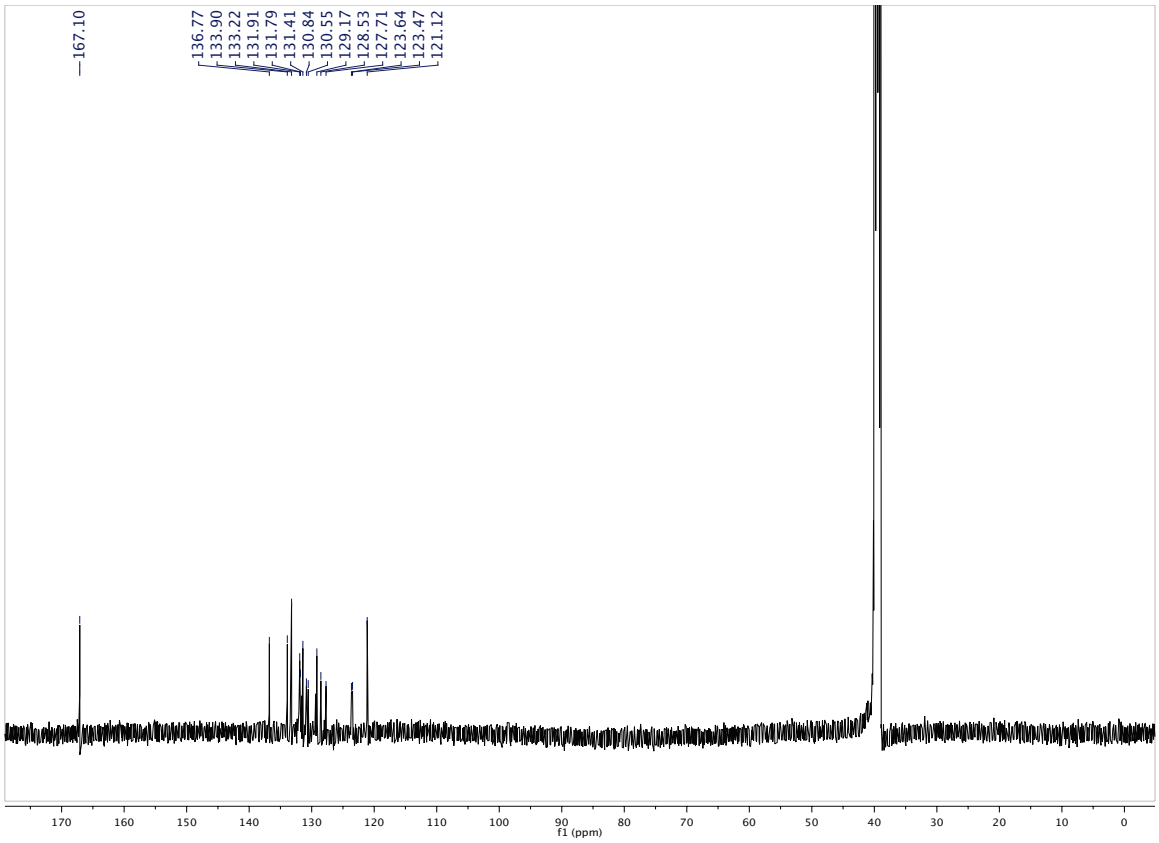
^{1}H NMR ($CDCl_3$) and ^{13}C NMR ($CDCl_3$) of Compound **7d**



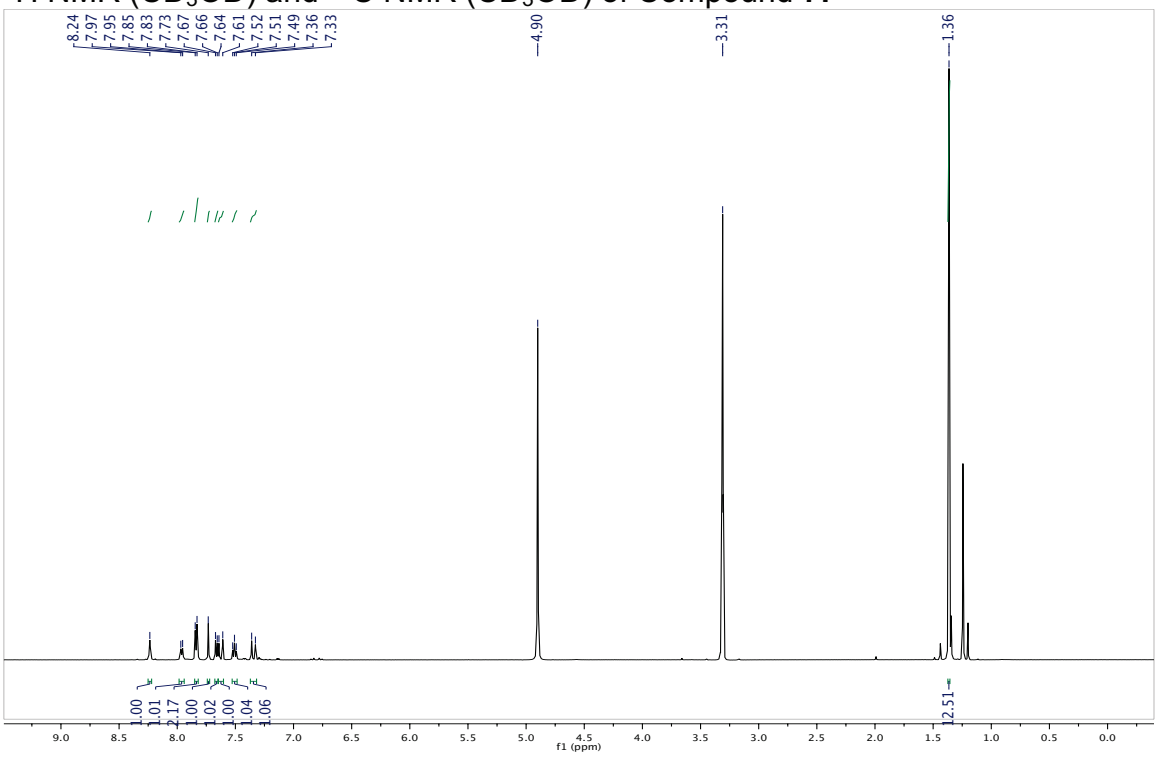


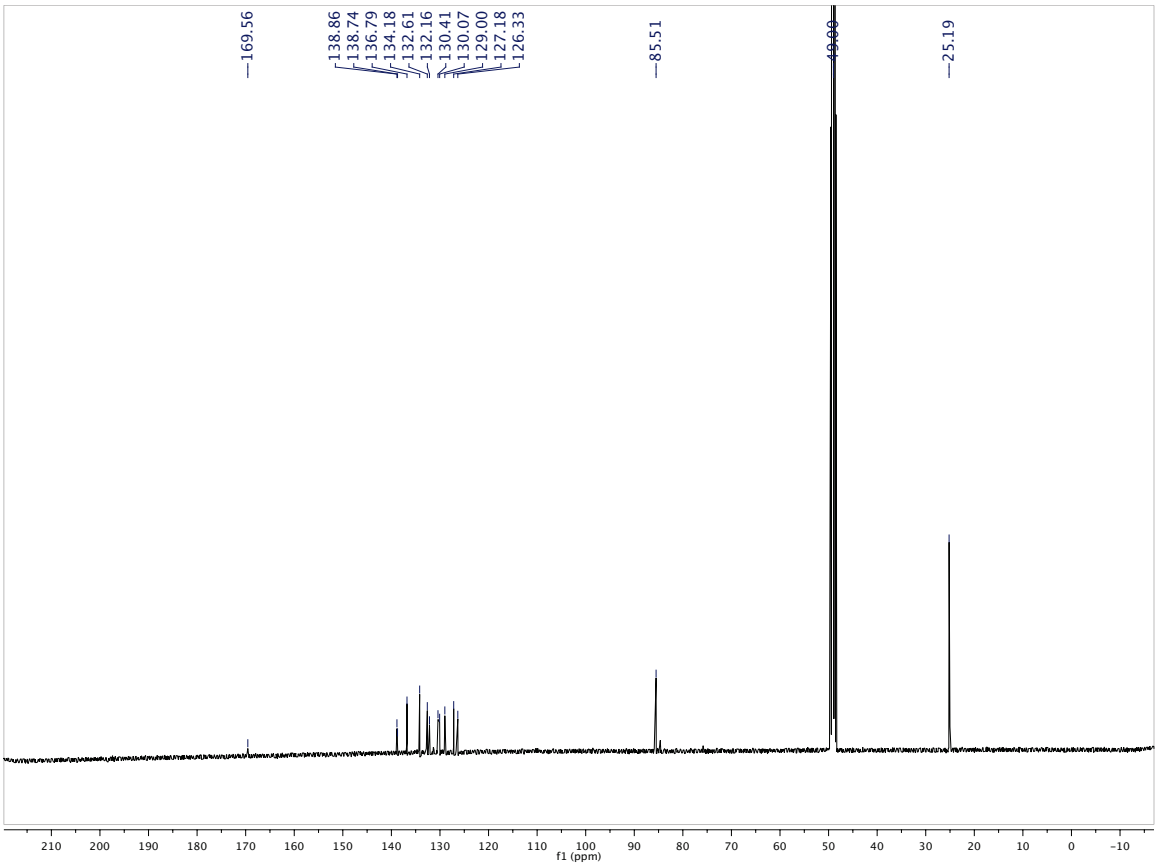
^{1}H NMR (DMSO) and ^{13}C NMR (DMSO) of Compound **7e**



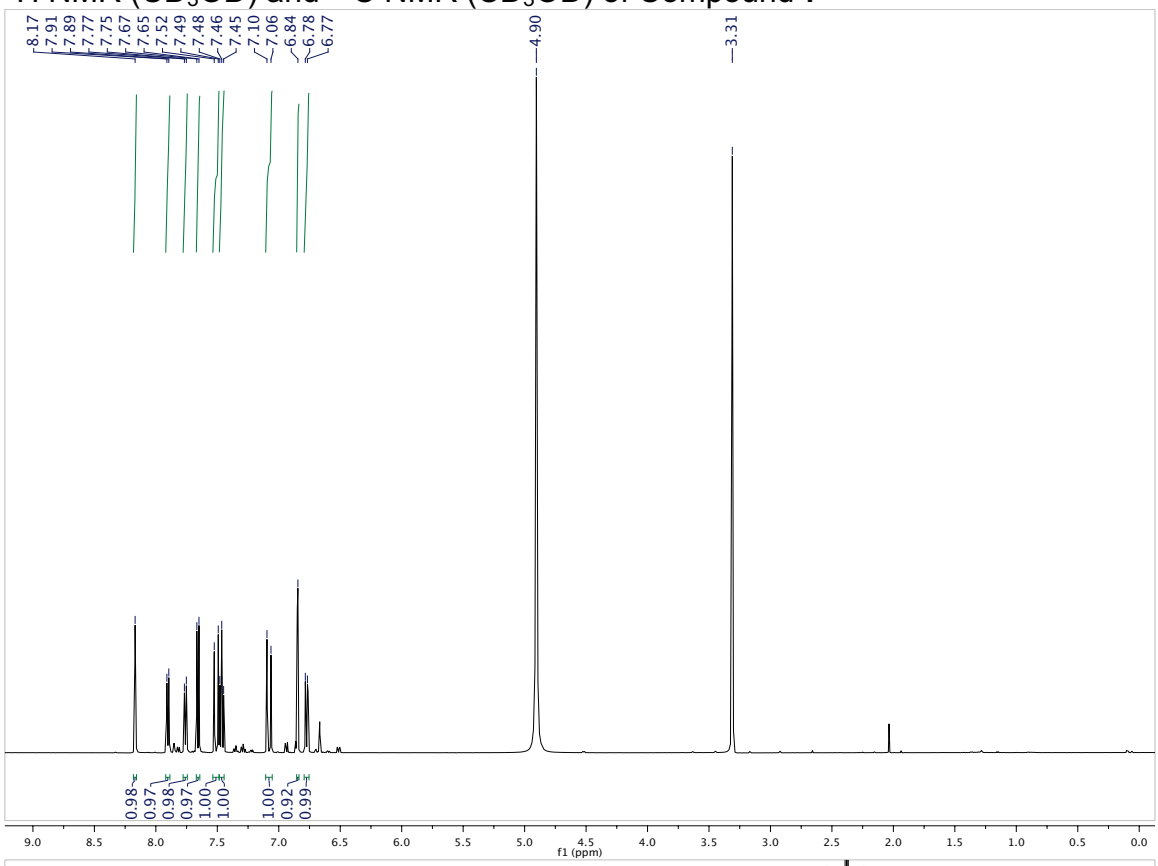


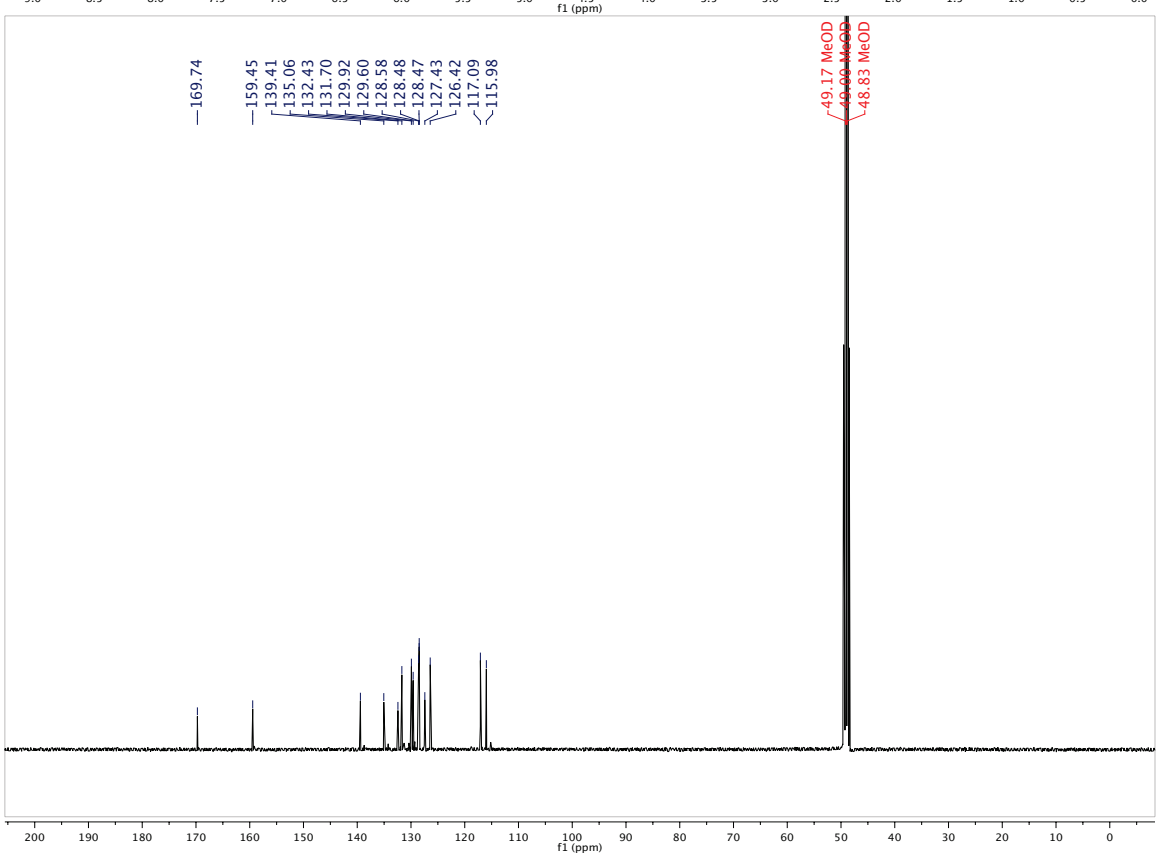
^{1}H NMR (CD_3OD) and ^{13}C NMR (CD_3OD) of Compound **7f**



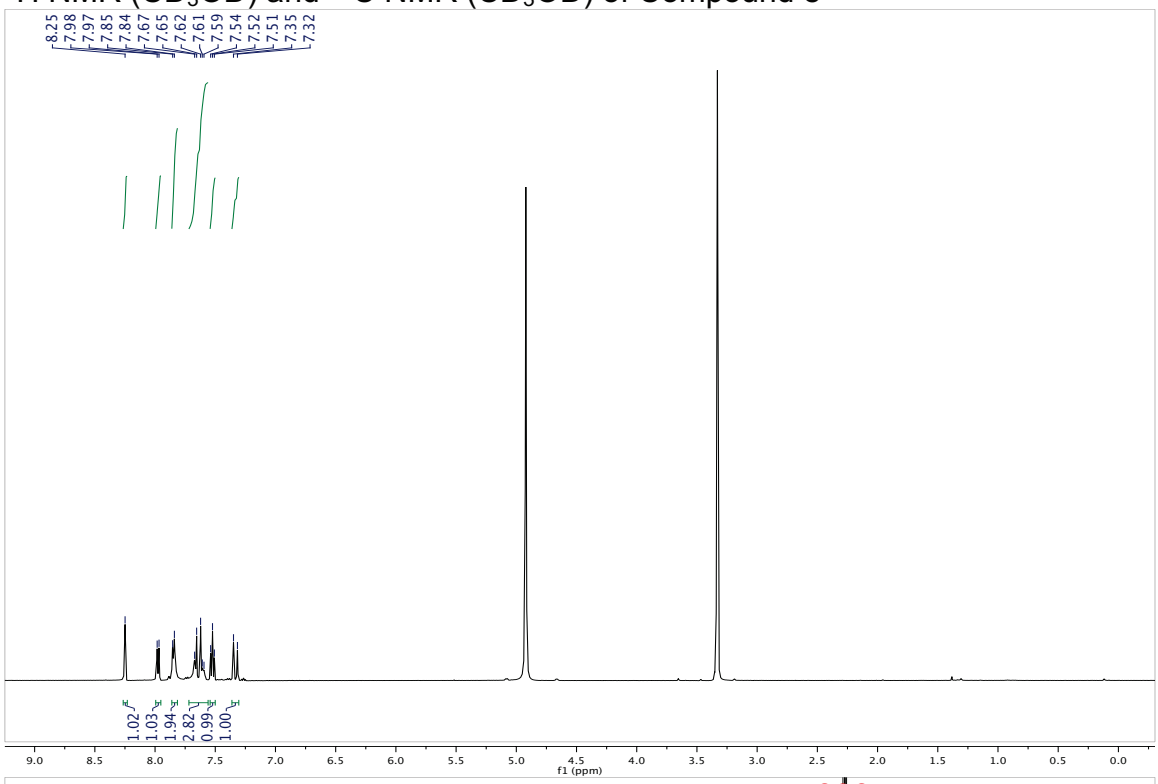


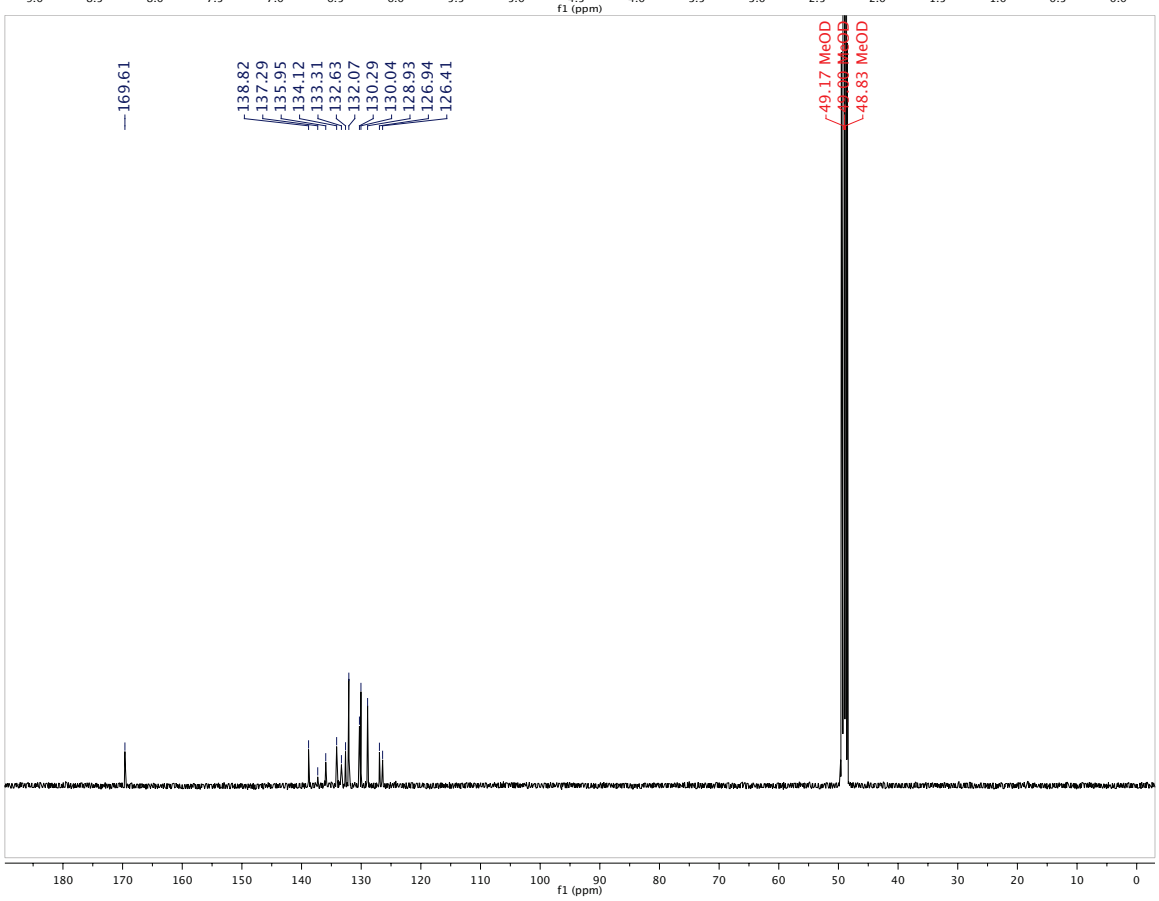
^{1}H NMR (CD_3OD) and ^{13}C NMR (CD_3OD) of Compound **7**



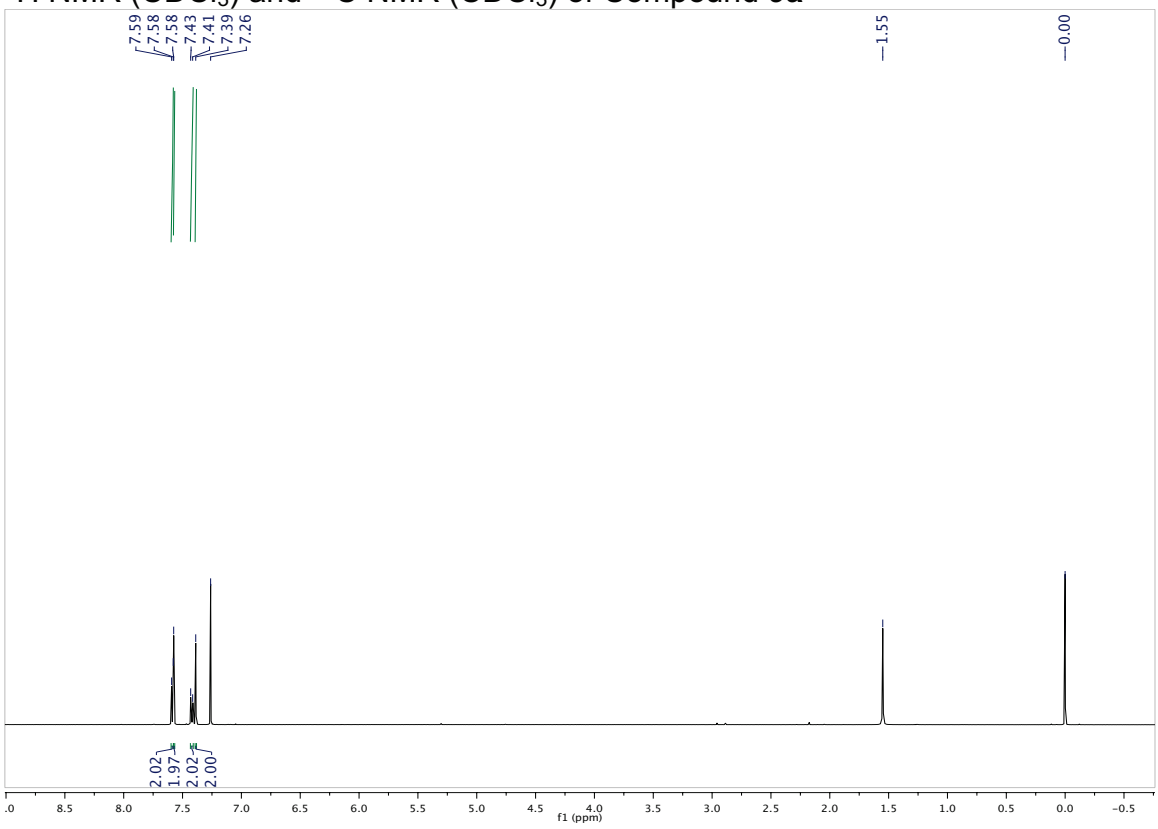


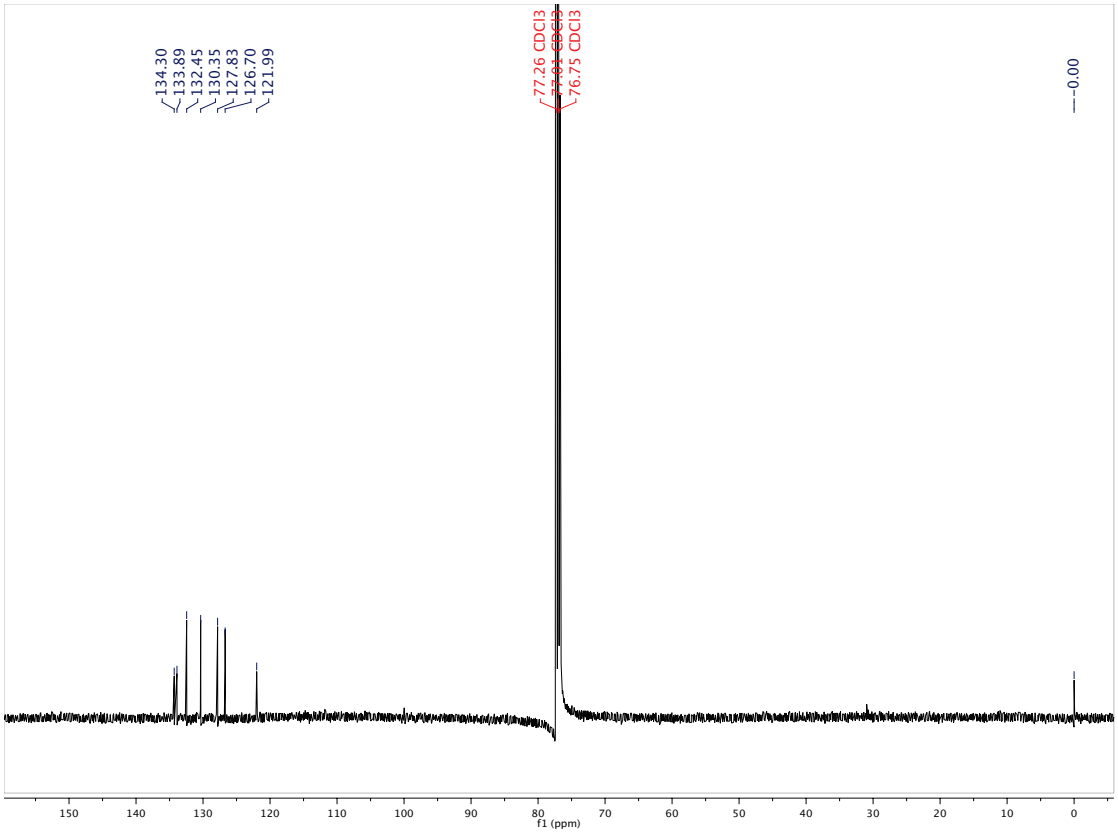
^{1}H NMR (CD_3OD) and ^{13}C NMR (CD_3OD) of Compound **8**



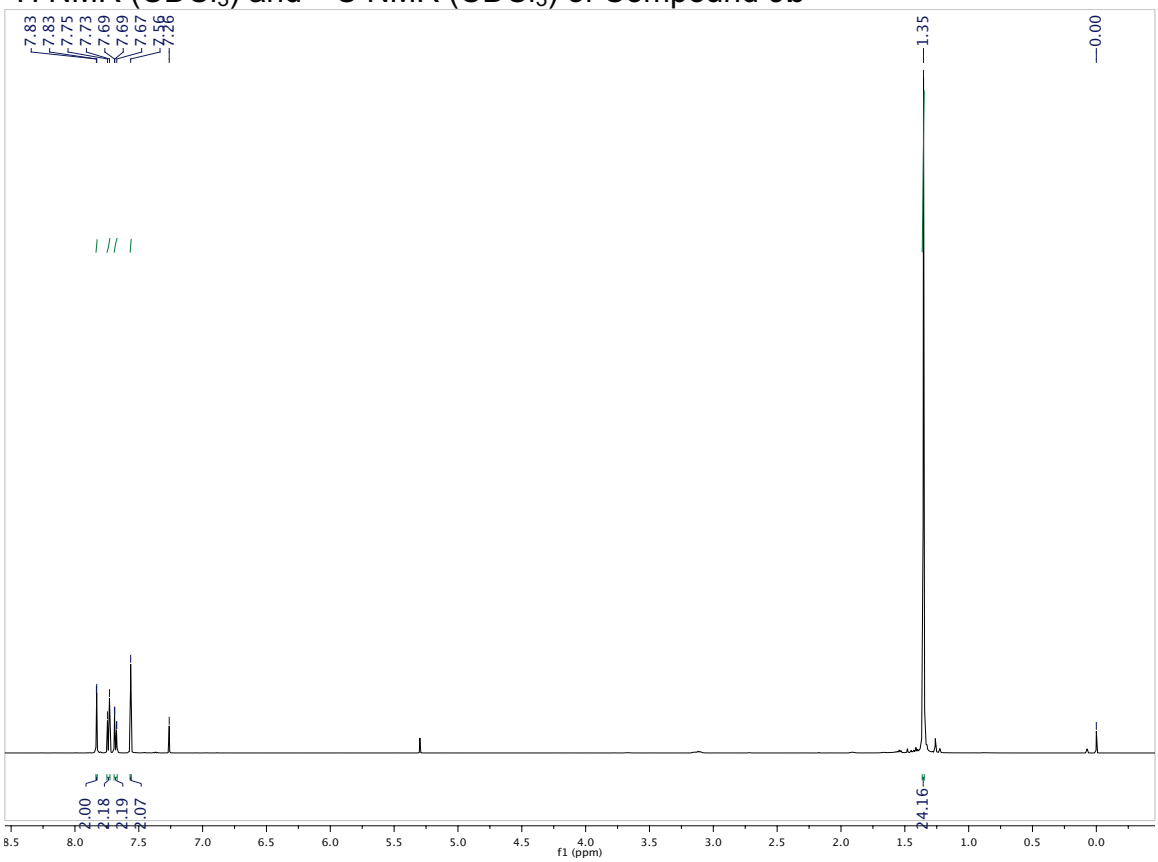


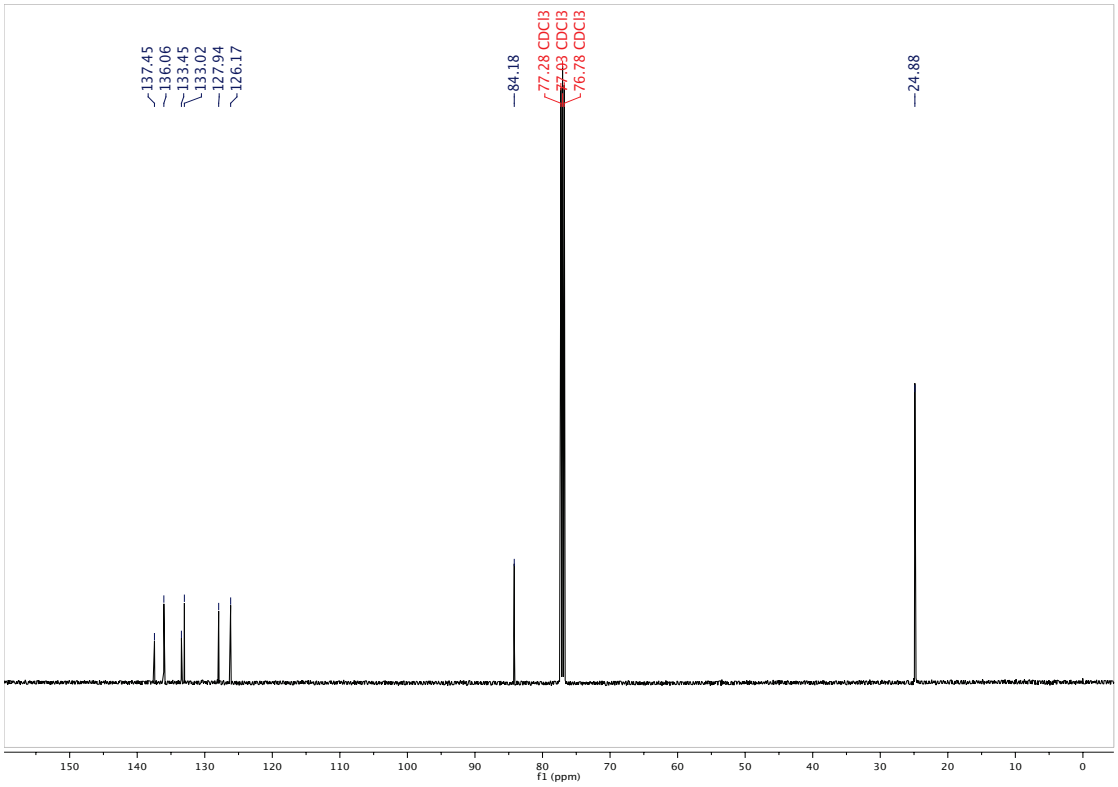
^{1}H NMR ($CDCl_3$) and ^{13}C NMR ($CDCl_3$) of Compound **9a**



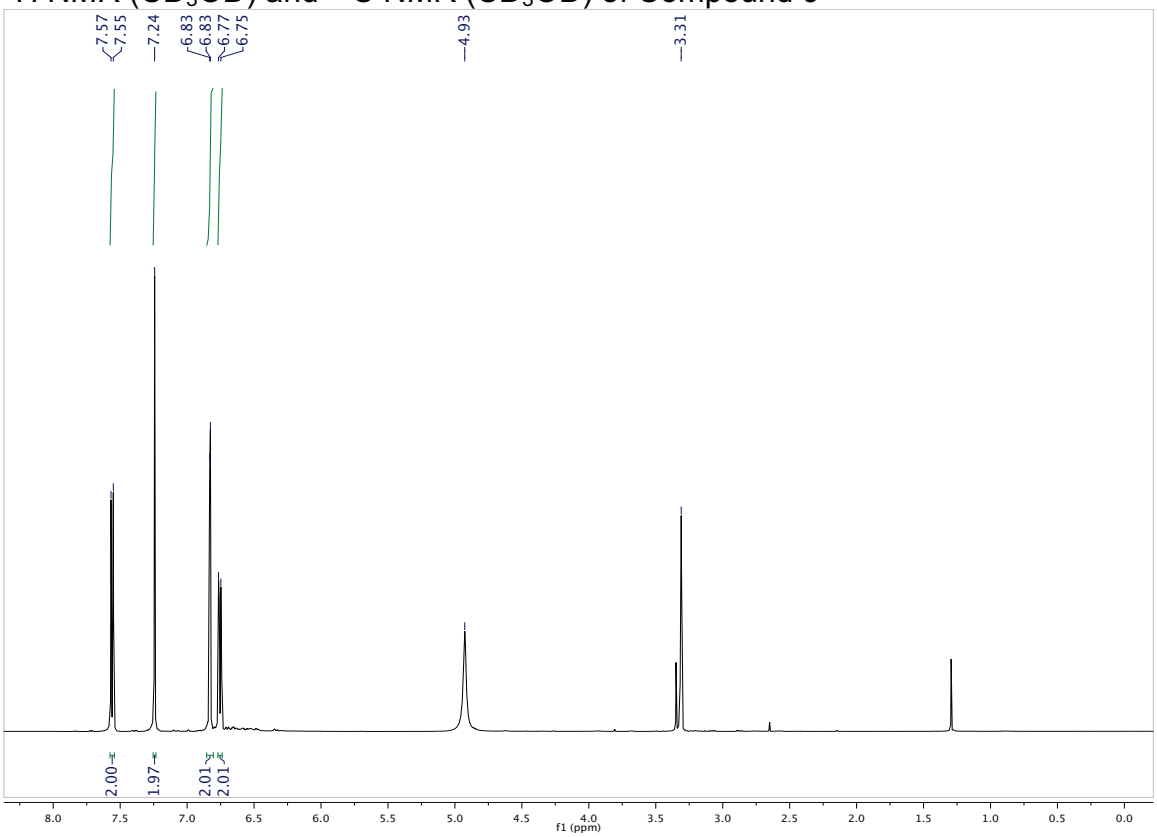


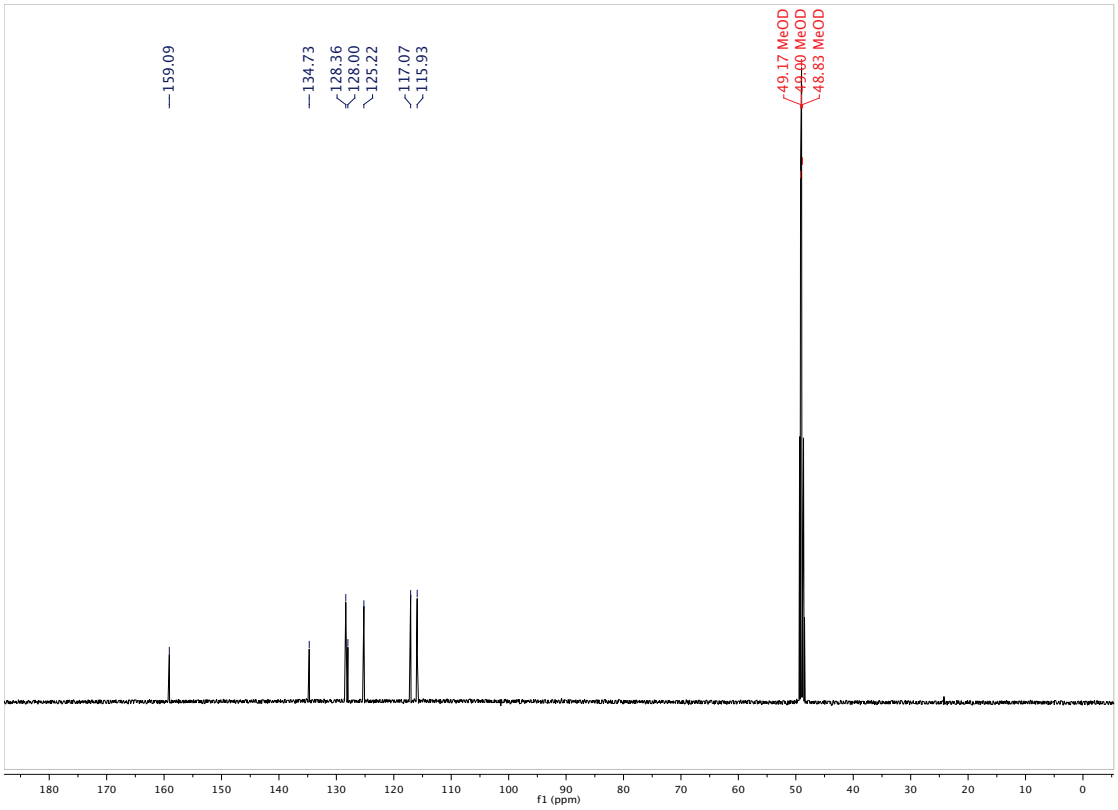
^{1}H NMR ($CDCl_3$) and ^{13}C NMR ($CDCl_3$) of Compound **9b**



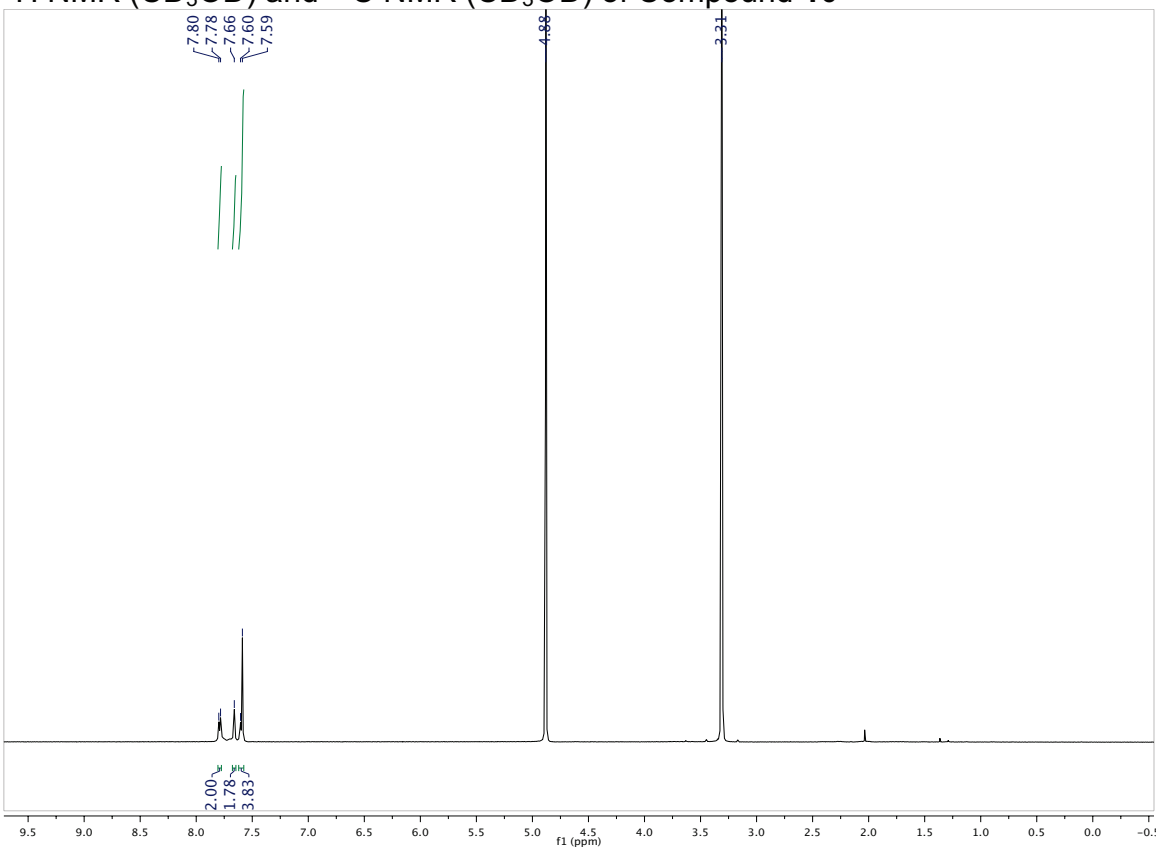


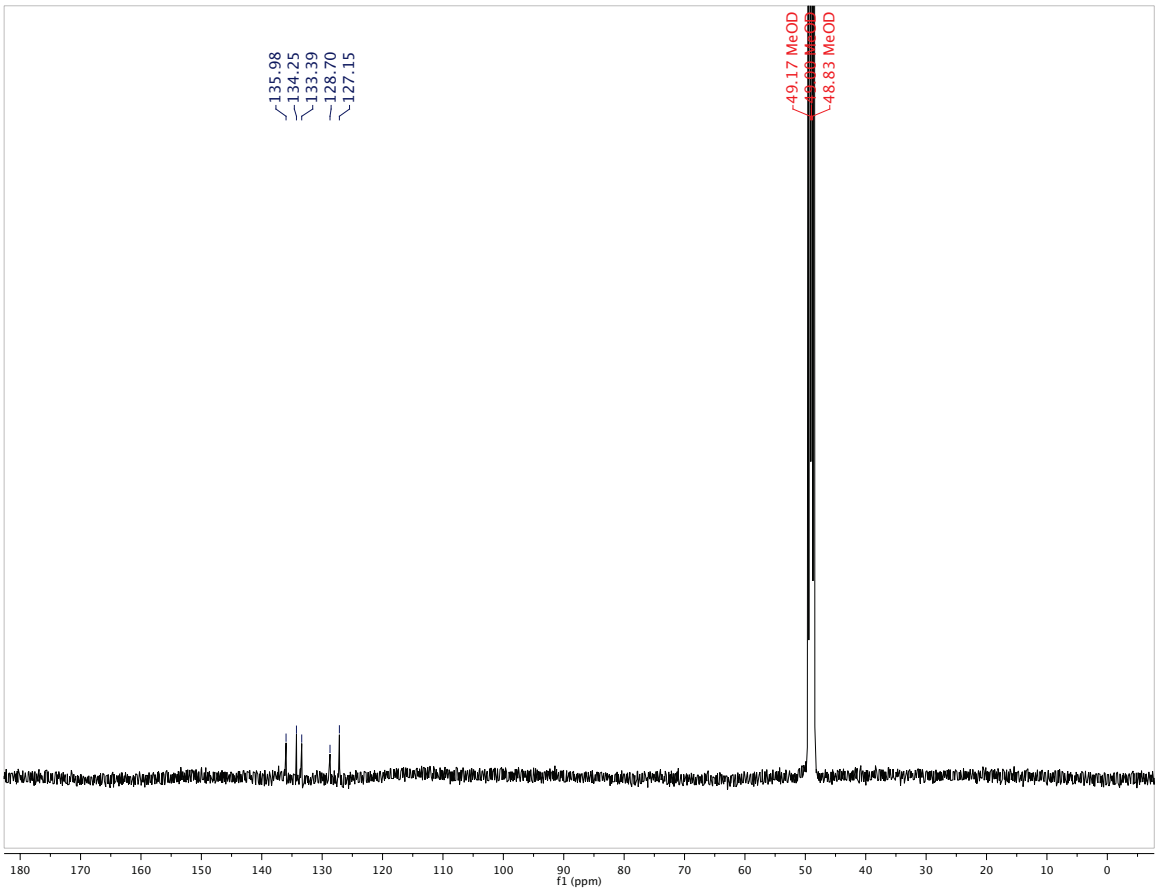
^{1}H NMR (CD_3OD) and ^{13}C NMR (CD_3OD) of Compound **9**



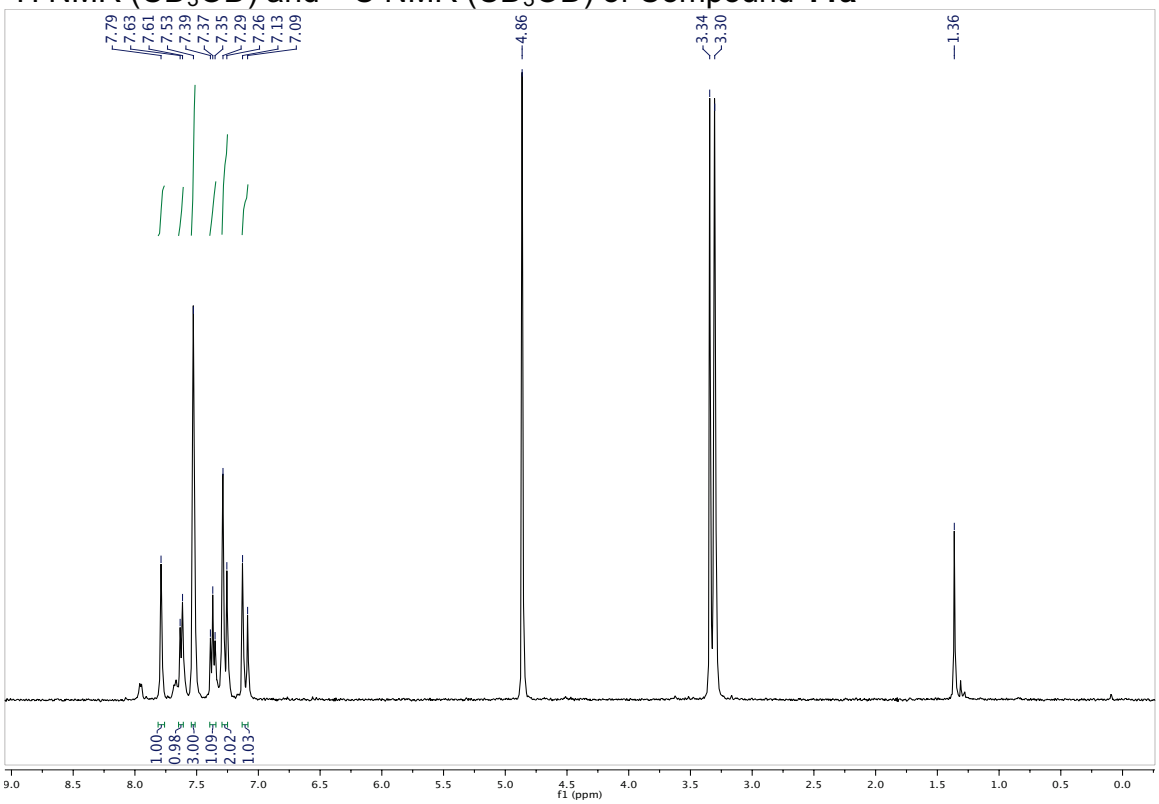


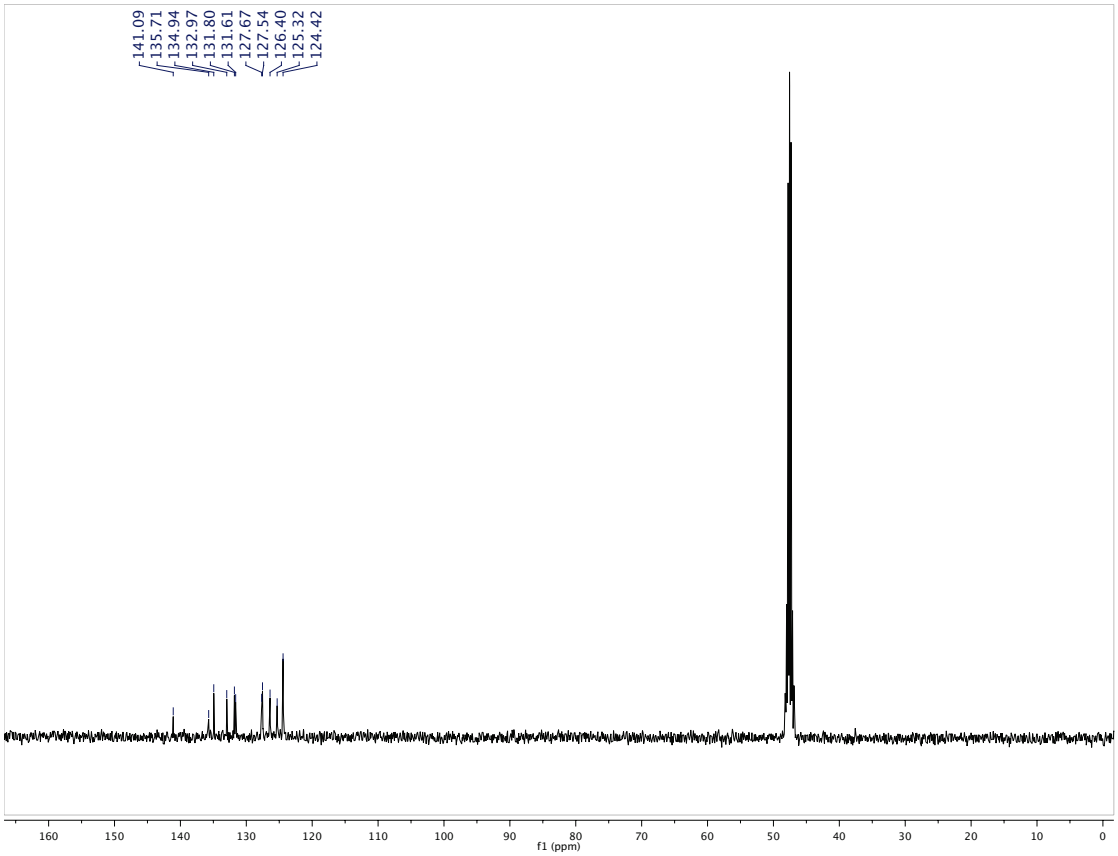
^{1}H NMR (CD_3OD) and ^{13}C NMR (CD_3OD) of Compound **10**



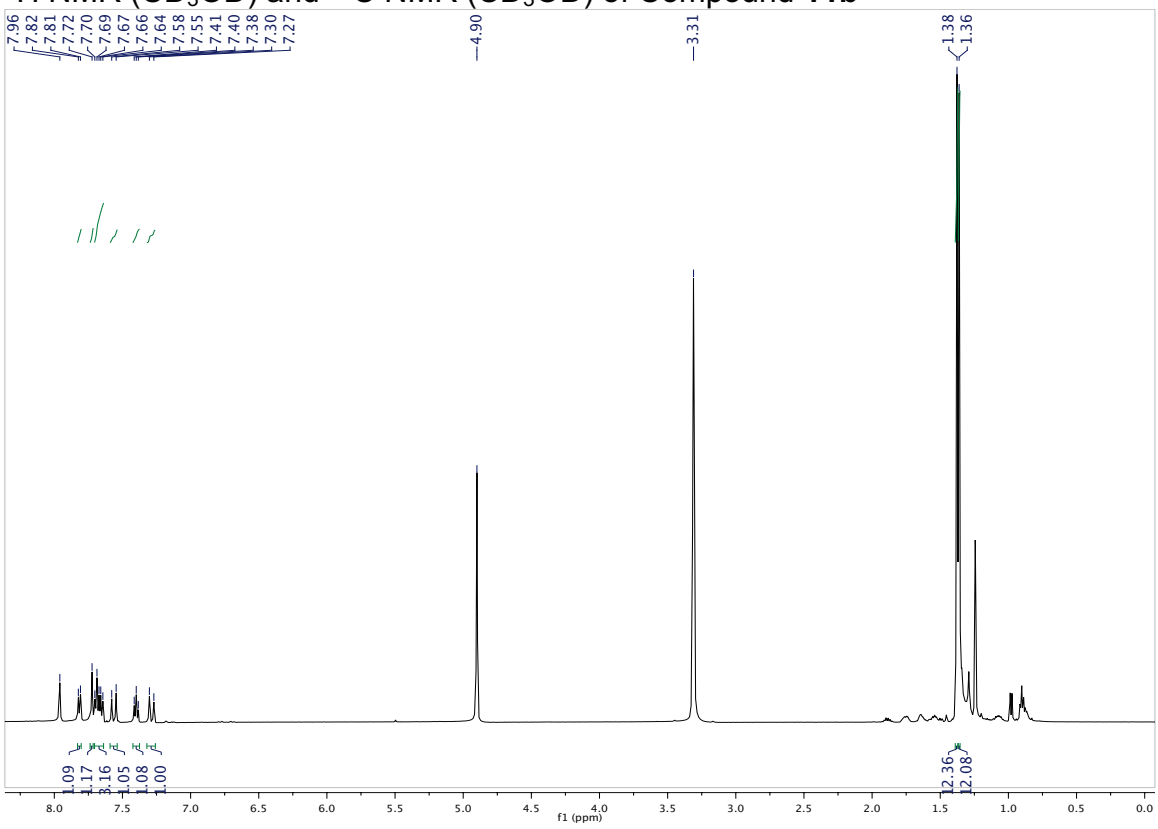


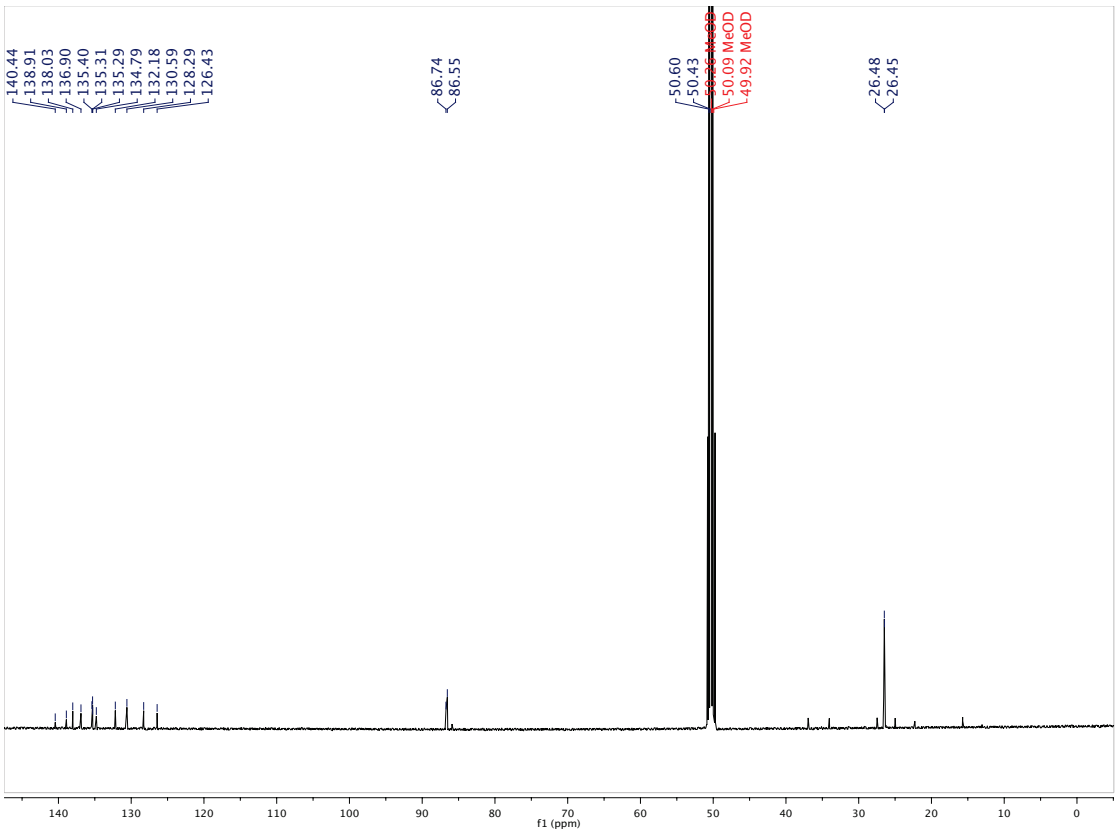
^{1}H NMR (CD_3OD) and ^{13}C NMR (CD_3OD) of Compound **11a**





^{1}H NMR (CD_3OD) and ^{13}C NMR (CD_3OD) of Compound **11b**





^{1}H NMR (CD_3OD) and ^{13}C NMR (CD_3OD) of Compound **11**