Supplementary Material

SAR Study on Novel Truxillic Acid Monoester -Based Inhibitors of Fatty Acid Binding Proteins as Next-Generation Antinociceptive Agents

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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
```

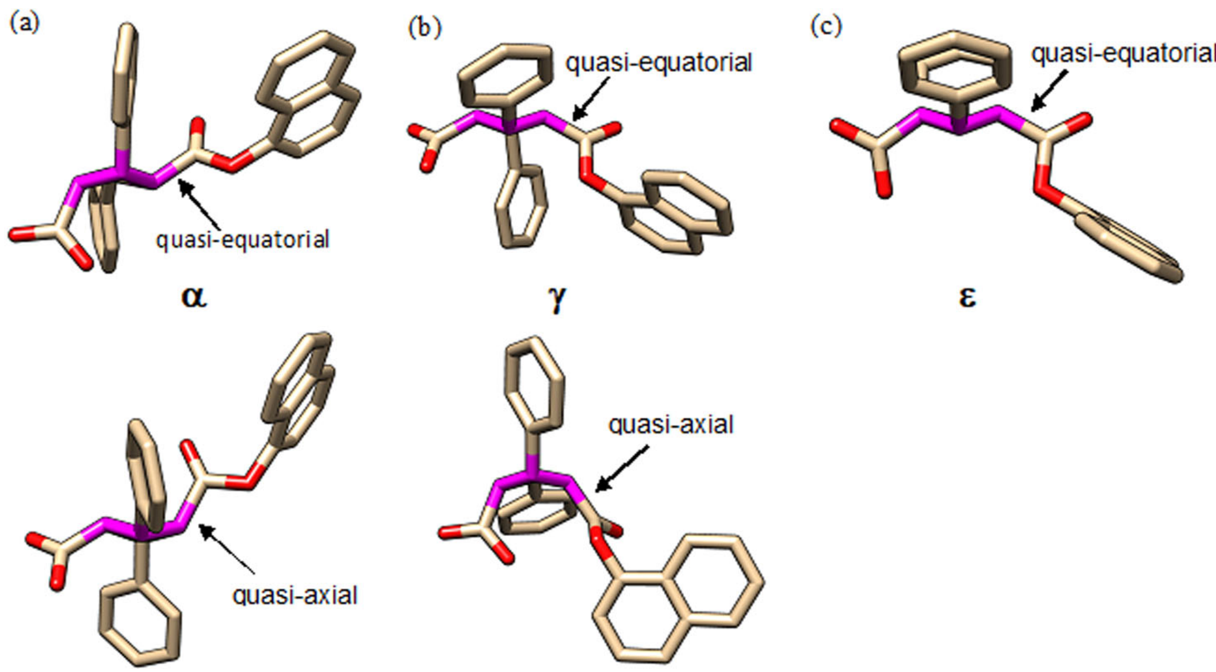


Figure S1. 3D structures of (a) α-**L1**, (b) γ-**L1** and (c) ε-**L1** isomers with its ester moiety in the quasi-equatorial or quasi-axial conformation for α-**L1** and γ-**L1**, and that in the quasi-equatorial conformation for ε-**L1** (quasi-axial configuration is energetically impossible due to severe steric clash).

Table S1. Internal energy *E* (kcal/mol) of (α, γ, ε)-**L1** in quasi-axial and quasi-equatorial ester conformations*

Isomer	quasi-axial ester	quasi-equatorial ester	ΔE
α	82.1	77.1	5.0
γ	92.0	81.0	11.0
ε	N/A	70.5	N/A

*Calculated at their energy minima using the MMFF94 forcefield. The energy minimum of the quasi-axial conformation of the ε-isomer was not found. This conformation is impossible to take due to serious steric clash.

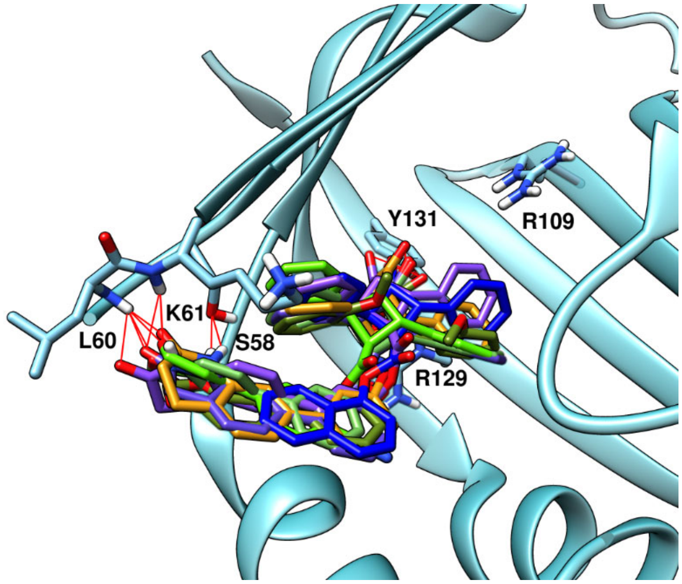


Figure S2. Docking pose of **L1** (dark blue), **α-1**, **α-5**, **α-7, α-8**, **α-9** and **α-10** at the canonical binding site (Tyr131-Arg129-Arg109) of FABP5 (cyan).

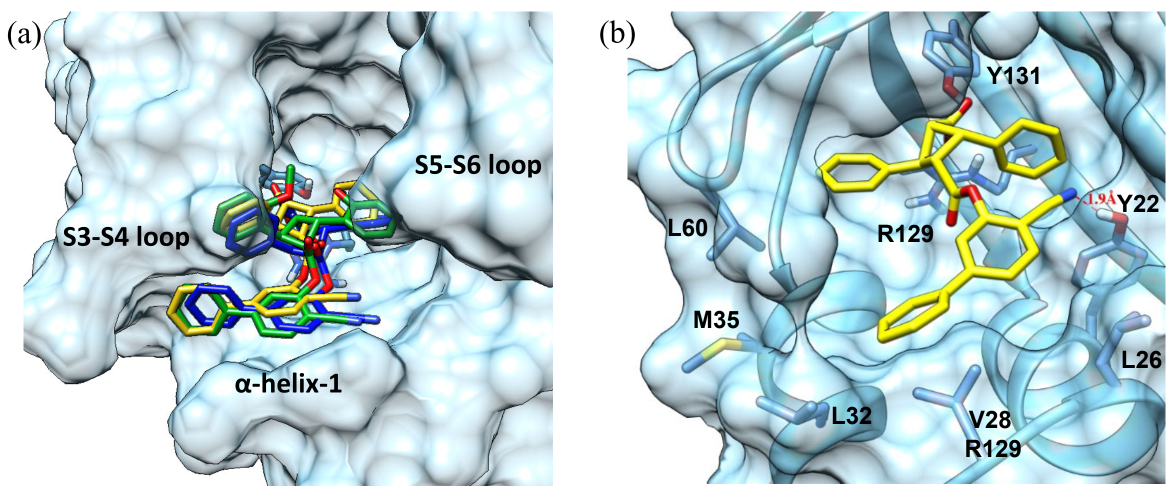


Figure S3. (a) Docking poses of **α-3** (yellow), **α-4** (green), and **γ-3** (dark blue) at the canonical binding site (Tyr131-Arg129, Arg109) of FABP5 (light blue); (b) Docking pose of **γ-3** (yellow) at the canonical binding site (Tyr131, Arg129) of FABP5 with an additional H-bonding of the cyano nitrogen with Tyr22.

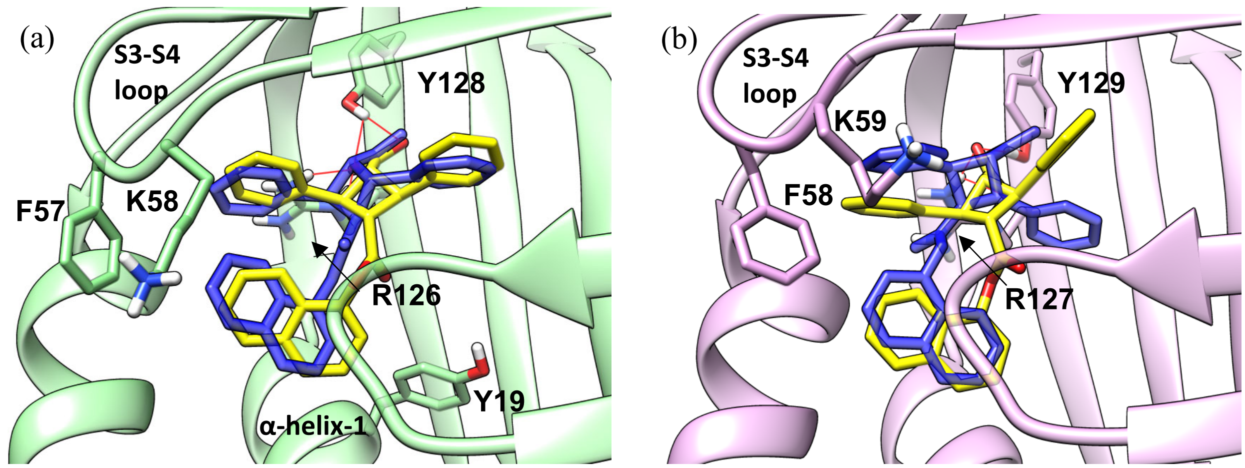


Figure S4. (a) Overlay of **ε-202** (yellow) and **L1** (blue) at the canonical binding site (Tyr128, Arg126) of FABP3 and (b) Overlay of **ε-202** (yellow) and **L1** (blue) at the canonical binding site (Tyr129, Arg127) of FABP7.

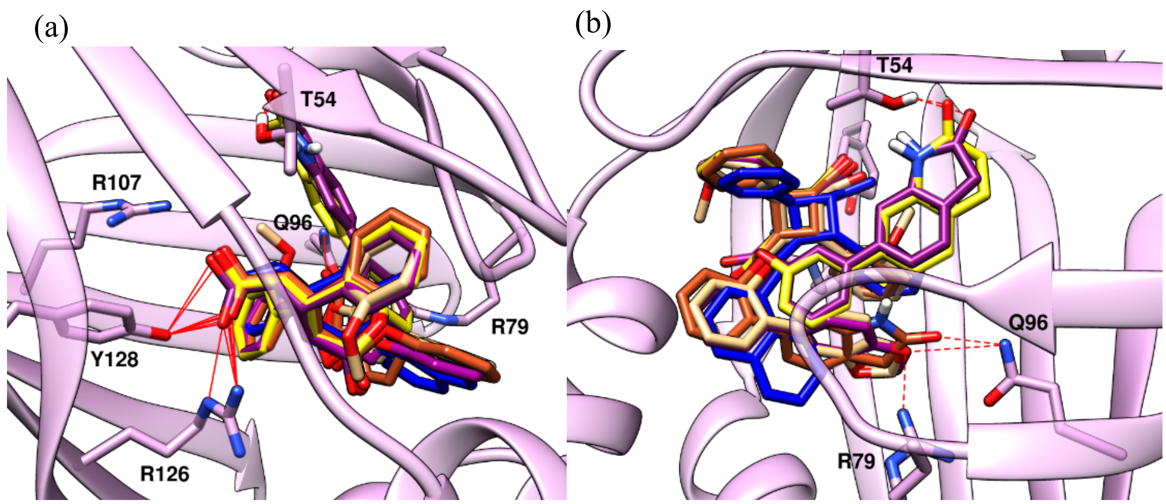


Figure S5. Docking poses of **α-2**, **α-18**, **α-11**, **α-8**, **α-1** and **L1** (cocrystal structure for comparison) at the canonical binding site (Tyr128, Arg126) of FABP7. (a) A view of the canonical interactions with Tyr128 and Arg126 (b) A view of the interactions of the H-bond acceptors in the distal biphenyl ester moieties with Thr54, Arg79, and Gln96.

(a) (b)

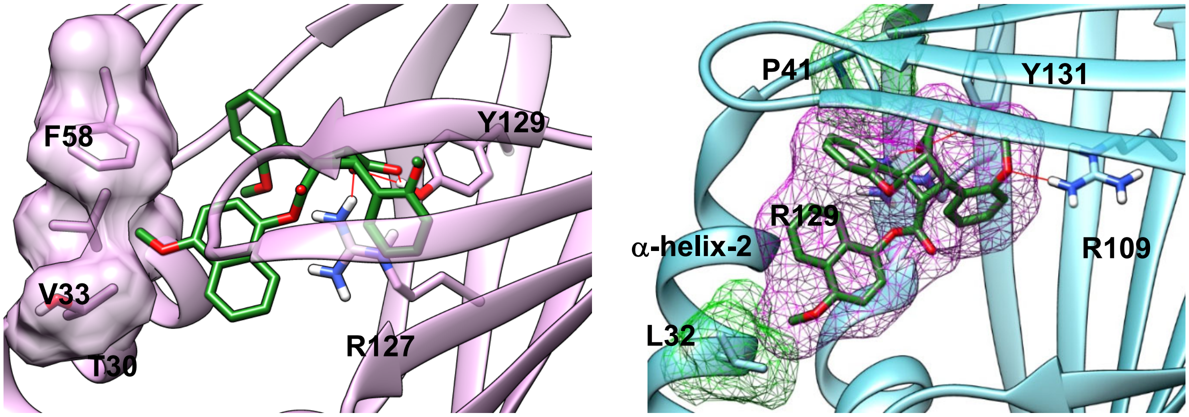


Figure S6. (a) Docking pose of **γ-109** (green) in the canonical binding site (Tyr129, Arg127) of FABP7. (b) Docking pose of **γ-109** (green) in FABP5. The clash of the 4-MeO group with Leu32 and Met35 in the α-helix-2 leads to the substantial weakening of the canonical interaction of the carboxylic acid moiety with Arg129 and Tyr131.

Table S2. Docking energy scores of TAMEs for FABP3, 5 and 7; pkCSM predictions of AMES, hERG1 and LD_{50} values; ClogP values predicted by ChemDraw.

	TAMEs	FABP5 Ki (μM)	FABP5 (kcal/mol)	FABP3 (kcal/mol)	FABP7 (kcal/mol)	AMES	hERG1	LD_{50} (mol/kg)	ClogP
1	**α-1**	0.12 ± 0.02	-10.18	-9.52	-10.55	Yes	No	3.58	5.36
2	**α-2**	0.29 ± 0.01	-9.49	-11.04	-11.99	Yes	No	3.42	4.80
3	**α-3**	0.32 ± 0.08	-9.47	-9.67	-11.17	No	No	2.85	6.22
4	**α-4**	0.33 ± 0.06	-8.62	-10.63	-11.06	No	No	2.92	5.26
5	**γ-3**	0.33 ± 0.02	-8.8	-10.54	-10.98	Yes	No	3.62	6.22
6	**α-5**	0.36 ± 0.05	-9.67	-9.01	-9.25	No	No	2.97	6.59
7	**α-6**	0.41 ± 0.15	-8.29*	-7.93	-10.92	No	No	3.06	5.58
8	**α-7**	0.44 ± 0.05	-9.65	-8.79	-11.44	No	No	2.79	4.45
9*	**L2**	0.55± 0.05	-8.47	-10.62	-10.23	Yes	No	2.90	5.12
10	**α-8**	0.59 ± 0.08	-10.55	-9.7	-11.23	No	No	2.79	5.95
11	**α-9**	0.72 ± 0.08	-8.45	-9.59	-9.7	No	No	2.62	5.62
12	**α-10**	0.74 ± 0.06	-9.82	-8.64	-10.34	No	No	2.85	5.95
13	**α-11**	0.79 ± 0.18	-8.96	-11.44	-11.34	No	No	2.96	6.03
14	**γ-12**	0.79 ± 0.08	-8.58	-8.45	-10.76	Yes	No	3.12	6.02
15*	**L1**	0.81 ± 0.09	-8.85	-10.34	-10.83	Yes	No	3.24	6.08
16	**α-12**	0.87 ± 0.06	-9.22	-10.23	-10.73	Yes	No	3.12	6.02
17	**γ-9**	0.89 ± 0.25	-9.1	-9.46	-10.26	No	No	2.62	5.62
18	**α-13**	1.03 ± 0.11	-8.51	-8.73	-9.52	Yes	No	2.90	5.97
19	**α-14**	1.06 ± 0.08	-10.04	-7.77	-8.12	Yes	No	3.06	4.39
20	**γ-6**	1.26 ± 0.12	-8.96	-9.46	-9.26	No	No	3.06	5.58
21	**α-15**	1.30 ± 0.09	-8.19	-8.3	-7.97	No	No	3.41	4.97
22	**α-16**	1.30 ± 0.28	-8.06	-10.12	-9.44	No	No	2.87	4.72
23	**γ-102**	1.39 ± 0.07	-8.22	-9.62	-10.28	No	No	2.84	5.66
24	**ε -11**	1.45 ± 0.26	-8.50	-9.75	-11.67	Yes	No	3.18	6.03
25	**α-17**	1.56 ± 0.19	-9.53	-6.56	-10.2	No	No	2.98	5.58
26	**α-18**	1.59 ± 0.11	-9.07	-10.66	-11.05	No	No	3.02	5.06
27	**α-19**	1.59 ± 0.24	-8.14	-11.13	-10.93	No	No	3.10	5.27
28	**ε-201**	1.65 ± 0.22	-8.45	-10.44	-10.03	Yes	No	3.50	6.98
29*	**L3**	1.72 ±0.12	-8.69	-8.69	-9.97	Yes	No	3.17	6.26
30	**α-20**	1.74 ± 0.08	-8.42	-8.52	-9.64	No	No	2.99	5.26
31	**α-21**	1.75 ± 0.07	-9.19	-9.12	-10.88	No	No	2.76	5.02
32	**γ-13**	1.77 ± 0.02	-8.2	-7.81	-10.23	No	No	2.94	5.59
33	**γ-103**	1.82 ± 0.66	-8.69	-9.12	-9.7	No	No	3.25	5.12
34	**α-22**	1.83 ± 0.27	-8.81	-7.73	-10.16	No	No	3.01	6.45
35	**α-23**	2.15 ± 0.17	-8.38	-8.84	-10.4	No	No	3.29	5.61
36	**γ-104**	2.21 ± 0.43	-8.37	-6.84	-10.35	Yes	No	3.62	5.36
37	**γ-20**	2.46 ± 0.19	-9.03	-8.24	-9.44	No	No	2.95	5.26
38	**γ-15**	2.56 ± 0.17	-8.07	-1.64	-6.93	No	No	3.85	4.97
39	**α-24**	2.64 ± 0.01	-9.01	-9.64	-10.86	Yes	No	3.46	6.57
40	**α-25**	2.81 ± 0.42	-9.63	-9.99	-11.00	No	No	3.02	5.02

41	**γ-105**	2.81 ± 0.57	-8.91	-7.82	-9.95	No	No	2.95	4.70
42	**ε-202**	3.03 ± 0.18	-8.08	-10.78	-9.87	No	No	2.82	6.08
43	**γ-1**	3.11 ± 0.62	-9.11	-8.80	-10.58	Yes	No	3.39	5.36
44	**ε-203**	3.15 ± 0.28	-10.32	-9.51	-10.84	No	No	3.56	6.55
45	**γ-8**	3.39 ± 0.34	-10.38	-10.13	-10.81	No	No	2.79	5.95
46	**ε-204**	3.40 ± 0.52	-9.64	-9.32	-10.51	No	No	2.92	6.93
47	**ε-5**	3.40 ± 0.56	-10.56	-9.26	-11.00	Yes	No	3.55	6.59
48	**γ-17**	3.69 ± 0.65	-9.36	-3.75	-9.57	Yes	No	2.76	5.58
49	**γ-106**	3.94 ± 0.43	-9.8	-9.39	-10.09	No	No	2.86	6.22
50	**ε-23**	5.08 ± 0.62	-9.33	-9.32	-10.51	Yes	No	3.46	6.57
51	**ε-206**	5.11 ± 0.84	-9.67	-9.26	-11.00	No	No	2.82	6.79
52	**γ-16**	6.6 ± .83	-8.08	-8.52	-9.29	No	No	2.71	4.72
53	**γ-10**	7.59 ± 1.11	-8.98*	-8.07	-9.78	No	No	2.85	5.95
54	**γ-107**	8.20 ± 1.54	-8.34	-7.86	-10.53	No	No	3.33	6.26
55	**ε-207**	8.38 ± 0.72	-8.74	-9.79	-9.56	No	No	2.72	5.68
56	**γ-108**	10.90 ± 2.81	-10.04	-8.39	-11.13	No	No	3.89	5.46
57	**α-26**	11.80 ± 1.64	-8.67	-6.06	-10.28	No	No	2.74	5.20
58	**γ-109**	26.61 ± 1.88	-8.36	-7.83	-9.68	Yes	No	2.70	5.03

*Docking energy score for (*R,R,R,R*)-enantiomer. Scores of all other α-isomers are for (*S,S,S,S*)-enantiomers and those of γ-isomers are for (1*S*,2*R*,3*S*,4*R*)-enantiomers.

Table S3. Swiss Target Prediction# for potential off-targets of selected FABP inhibitors

α-1	Known Actives (3D)*	α-2	Known Actives (3D)*	γ-3	Known Actives (3D)*	α-16	Known Actives (3D)*	α-19	Known Actives (3D)*
G protein-coupled receptor 44	888	G protein-coupled receptor 44	1234	G protein-coupled receptor 44	1048	Peroxisome proliferator-activated receptor gamma	1031	Peroxisome proliferator-activated receptor gamma	851
Cholecystokinin B receptor (by homology)	497	Endothelin receptor ET-A	654	Integrin alpha-4/beta-1	730	Integrin alpha-4/beta-1	710	Cholecystokinin B receptor	400
5-lipoxygenase activating protein	362	Cholecystokinin B receptor	458	Cholecystokinin B receptor (by homology)	468	Angiotensin-converting enzyme	420	Angiotensin-converting enzyme (by homology)	393
Lysosomal protective protein	331	Angiotensin-converting enzyme (by homology)	387	Angiotensin-converting enzyme (by homology)	376	Cholecystokinin B receptor (by homology)	418	Lysosomal protective protein	358
Endothelin receptor ET-A	318	Thromboxane A2 receptor	357	5-lipoxygenase activating protein	366	Lysosomal protective protein	372	Thromboxane A2 receptor	292
Caspase-1	298	Lysosomal protective protein	356	Lysosomal protective protein	362	5-lipoxygenase activating protein	310	Integrin alpha-V/beta-3	285
Peroxisome proliferator-activated receptor delta	285	Thromboxane-A synthase	311	Integrin alpha-V/beta-3	307	Integrin alpha-V/beta-3	296	Type-1 angiotensin II receptor (by homology)	246
Thromboxane-A synthase	280	Prostanoid EP4 receptor	299	Type-1 angiotensin II receptor (by homology)	305	Type-1 angiotensin II receptor (by homology)	284	p53-binding protein Mdm-2	217
Prostanoid DP receptor	243	5-lipoxygenase activating protein	269	Matrix metalloproteinase 3	274	Integrin alpha-4/beta-7	254	Thromboxane-A synthase	216
Angiotensin-converting enzyme	228	Caspase-1	268	Caspase-1	271	Matrix metalloproteinase 3	248	Caspase-1	213
Thromboxane A2 receptor	227	Type-1 angiotensin II receptor	263	Integrin alpha-4/beta-7	254	Caspase-1	246	5-lipoxygenase activating protein	203
Type-1 angiotensin II receptor (by homology)	214	Endothelin receptor ET-B	238	Thromboxane A2 receptor	242	Thromboxane-A synthase	239	Dihydroorotate dehydrogenase	167
Caspase-3	210	Prostanoid EP2 receptor	226	Thromboxane-A synthase	240	p53-binding protein Mdm-2	217	Matrix metalloproteinase 3	160
Carnitine O-palmitoyltransferase 1, liver isoform	169	Caspase-3	194	Dihydroorotate dehydrogenase	218	Dihydroorotate dehydrogenase	197	Peroxisome proliferator-activated receptor delta	151
Integrin alpha-4	155	Carnitine O-palmitoyltransferase 1, liver isoform	185	p53-binding protein Mdm-2	199	Matrix metalloproteinase 1	180	Caspase-3	143
Purinergic receptor P2Y12	147	Matrix metalloproteinase 1	148	Prostanoid DP receptor (by homology)	193	Caspase-3	156	Carnitine O-palmitoyltransferase 1, liver isoform	137
Diacylglycerol O-acyltransferase 1	141	Endothelin-converting enzyme 1	145	Matrix metalloproteinase 1	192	Endothelin-converting enzyme 1	150	Endothelin-converting enzyme 1	136
Phosphodiesterase 4B	132	Prostaglandin E synthase	143	Caspase-3	192	Carnitine O-palmitoyltransferase 1, liver isoform	141	Liver glycogen phosphorylase	130
Carbonic anhydrase II	127	Phosphodiesterase 4B	143	Endothelin-converting enzyme 1	161	Liver glycogen phosphorylase	132	Matrix metalloproteinase 1	124
Carnitine O-palmitoyltransferase 1, muscle isoform	109	Liver glycogen phosphorylase	124	Liver glycogen phosphorylase	137	Chymase	131	Induced myeloid leukemia cell differentiation protein Mcl-1	122
Endothelin-converting enzyme 1	107	Integrin alpha-4	124	Integrin alpha-4	131	Arachidonate 5-lipoxygenase	126	Chymase	118
Cytosolic phospholipase A2	104	Induced myeloid leukemia cell differentiation protein Mcl-1	123	Carnitine O-palmitoyltransferase 1, liver isoform	127	Prostaglandin E synthase	120	Arachidonate 5-lipoxygenase	116

Thrombin and coagulation factor X	103	Chymase	123	Glucagon receptor	125	Protein farnesyltransferase	106	Prostaglandin E synthase	108
T-cell protein-tyrosine phosphatase	102	Carnitine O-palmitoyltransferase 1, muscle isoform	123	Induced myeloid leukemia cell differentiation protein Mcl-1	125	Integrin alpha-4	105	Squalene synthetase (by homology)	99
Prostaglandin E synthase	99	Phosphodiesterase 4D	106	Purinergic receptor P2Y12	106	Carnitine O-palmitoyltransferase 1, muscle isoform	95	Protein farnesyltransferase	98
Phosphodiesterase 4D	96	Glycogen synthase kinase-3 beta	94	Chymase	104	ADAMTS5	93	Carnitine O-palmitoyltransferase 1, muscle isoform	96
Endothelin receptor ET-B	95	Bile acid receptor FXR	89	Transient receptor potential cation channel subfamily M member 8	91	Phosphodiesterase 4B	92	Integrin alpha-4	86
Caspase-7	83	Phospholipase A2 group IIA	88	Cholecystokinin A receptor	89	Cholecystokinin A receptor (by homology)	87	ADAMTS5	82
Casein kinase II alpha	81	Cholecystokinin A receptor	88	ADAMTS5	89	Glucagon receptor	78	Protein-tyrosine phosphatase 1B	81
Carbonic anhydrase I	73	Cytosolic phospholipase A2	82	Apoptosis regulator Bcl-X	83	Phosphodiesterase 4D	73	Cholecystokinin A receptor	80
Chymase	70	ADAMTS5	78	Matrix metalloproteinase 14	77	Bile acid receptor FXR	71	Matrix metalloproteinase 14	67
Glycogen synthase kinase-3 beta	66	Caspase-7	72	MAP kinase p38 alpha	77	Matrix metalloproteinase 14	69	Cytosolic phospholipase A2	61
Apoptosis regulator Bcl-X	66	Prostanoid EP3 receptor	72	Adenosine A1 receptor	77	Phospholipase A2 group IIA	68	Apoptosis regulator Bcl-X	56
FK506-binding protein 1A	63	P2X purinoceptor 3	67	Caspase-7	76	Apoptosis regulator Bcl-X	64	MAP kinase p38 alpha	56
Integrin alpha-5/beta-1	61	Carnitine palmitoyltransferase 2	62	Bile acid receptor FXR	72	Angiotensin II receptor	59	Peptidyl-prolyl cis-trans isomerase NIMA-interacting 1	54
Induced myeloid leukemia cell differentiation protein Mcl-1	59	Thrombin and coagulation factor X	60	Phosphodiesterase 10A	70	MAP kinase p38 alpha	56	Glucagon receptor	54
Glucagon	58	ADAM17	59	Thrombin and coagulation factor X	70	P2X purinoceptor 3	55	Angiotensin II receptor	53
Protein-tyrosine phosphatase 2C	55	Peptidyl-prolyl cis-trans isomerase NIMA-interacting 1	58	Angiotensin II receptor	65	Serine/threonine-protein kinase Aurora-A	50	Serine/threonine-protein kinase Aurora-A	51
Integrin alpha-V/beta-5	53	Angiotensin II receptor	54	Caspase-8	62	Carnitine palmitoyltransferase 2	50	Carnitine palmitoyltransferase 2	50
Geranylgeranyl transferase type I	52	T-cell protein-tyrosine phosphatase	51	Methionine aminopeptidase 2	61	Caspase-8	48	Caspase-7	49
Hexokinase type IV	51	Cyclin-dependent kinase 5/CDK5 activator 1	51	Glycogen synthase kinase-3 beta	59	Fatty acid binding protein adipocyte	47	Caspase-8	48
Phosphodiesterase 10A	49	Adenosine A1 receptor	51	Peptidyl-prolyl cis-trans isomerase NIMA-interacting 1	57	Integrin alpha-IIb/beta-3	43	Hydroxycarboxylic acid receptor 2	47
Adenosine A1 receptor	47	Leukocyte elastase	51	Apoptosis regulator Bcl-2	52	Cannabinoid receptor 2	42	Cannabinoid receptor 2	43
Tyrosine-protein kinase SYK	43	FK506-binding protein 1A	50	Epidermal growth factor receptor erbB1	49	Integrin alpha-5/beta-1	40	Fatty acid binding protein adipocyte	42
Hematopoietic cell protein-tyrosine phosphatase 70Z-PEP	41	Apoptosis regulator Bcl-2	45	FK506-binding protein 1A	48	Angiotensin-converting enzyme 2	40	Complement factor D	39
Leukocyte elastase	41	Fatty acid binding protein adipocyte	43	Tyrosine-protein kinase SYK	46	Hydroxycarboxylic acid receptor 2	39	Adenosine A2a receptor (by homology)	37
Intercellular adhesion molecule (ICAM-1), Integrin alpha-L/beta-2	37	Protein-tyrosine phosphatase 2C	43	Prostanoid IP receptor	44	Matrix metalloproteinase 7	37	Cannabinoid receptor 1	34

Complement factor D	36	Complement factor D	42	Cyclin-dependent kinase 5/CDK5 activator 1	44	Complement factor D	35	Angiotensin-converting enzyme 2	32
Neurotensin receptor 1	36	Purinergic receptor P2Y12	39	Complement factor D	42	Protein-tyrosine phosphatase 2C	32	Integrin alpha-5/beta-1	31
Signal transducer and activator of transcription 3 (by homology)	35	Thymidylate synthase	39	Hydroxycarboxylic acid receptor 2	42	Cannabinoid receptor 1	31	FK506-binding protein 1A	31

* Known active compounds with >0.85 Tanimoto similarity.

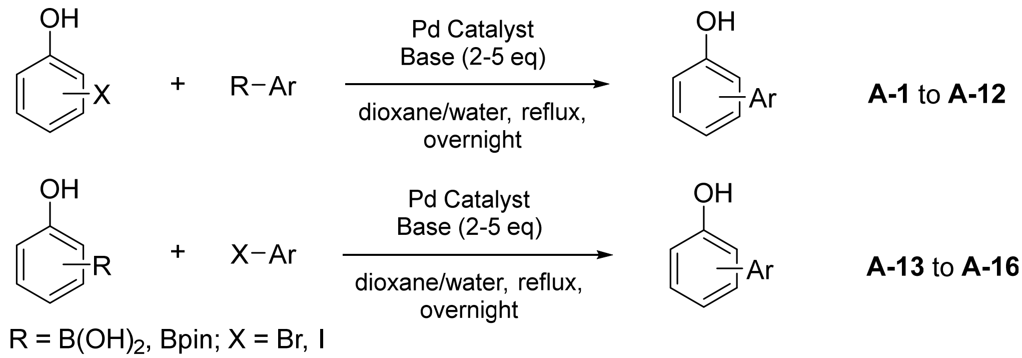
http://www.swisstargetprediction.ch

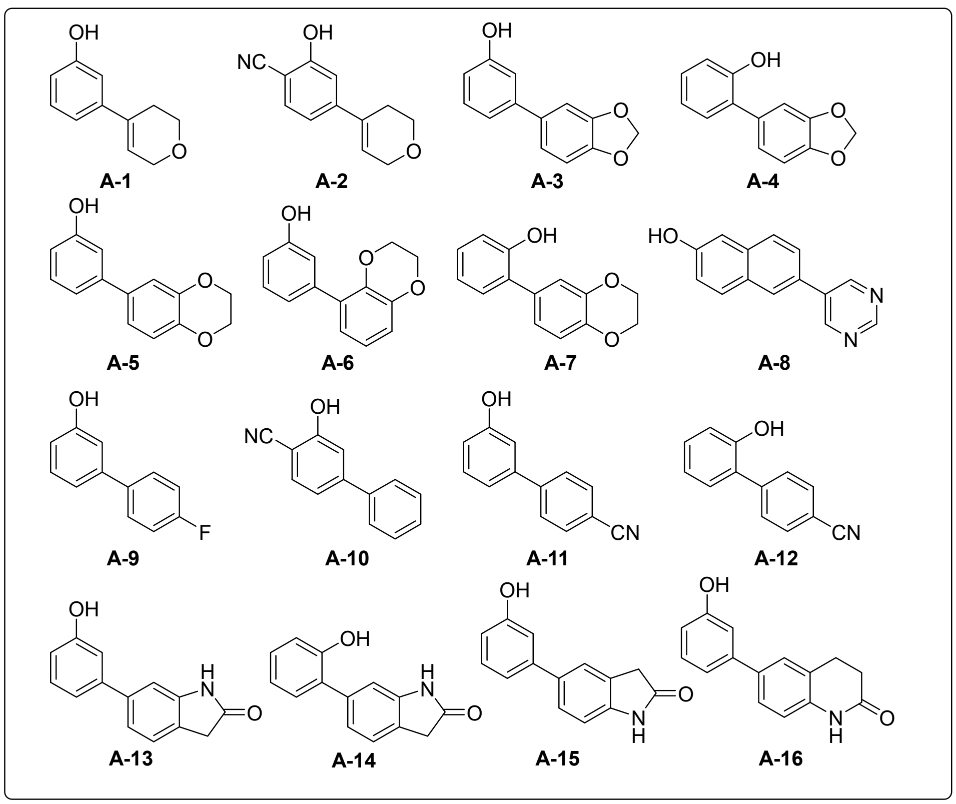
Table S4. Swiss Target Prediction for the probability of interactions between selected FABP inhibitors and potential off-targets based on the number of known actives

TAME	Target	Probability*	Known actives (3D)
α-1	G protein-coupled receptor 44	0.122	888
	Cholecystokinin B receptor (by homology)	0.122	497
	5-lipoxygenase activating protein	0.122	362
	Lysosomal protective protein	0.122	331
	Endothelin receptor ET-A	0.122	318
	Caspase-1	0.122	298
	Peroxisome proliferator-activated receptor delta	0.122	285
	Thromboxane-A synthase	0.122	280
	Prostanoid DP receptor	0.122	243
	Angiotensin-converting enzyme	0.122	228
α-2	G protein-coupled receptor 44	0.122	1234
	Cholecystokinin B receptor	0.122	458
	Angiotensin-converting enzyme (by homology)	0.122	387
	Thromboxane A2 receptor	0.122	357
	Lysosomal protective protein	0.122	356
	Thromboxane-A synthase	0.122	311
	Prostanoid EP4 receptor	0.122	299
	5-lipoxygenase activating protein	0.122	269
	Caspase-1	0.122	268
	Type-1 angiotensin II receptor	0.122	263
γ-3	G protein-coupled receptor 44	0.103	1048
	Integrin alpha-4/beta-1	0.103	730
	Cholecystokinin B receptor (by homology)	0.103	468
	Angiotensin-converting enzyme (by homology)	0.103	376
	5-lipoxygenase activating protein	0.103	366
	Integrin alpha-V/beta-3	0.103	307
	Type-1 angiotensin II receptor (by homology)	0.103	305
	Matrix metalloproteinase 3	0.103	274
	Caspase-1	0.103	271
	Integrin alpha-4/beta-7	0.103	254
α-16	Peroxisome proliferator-activated receptor gamma	0.111	1031
	Integrin alpha-4/beta-1	0.111	710
	Angiotensin-converting enzyme	0.111	420
	Cholecystokinin B receptor (by homology)	0.111	418
	Lysosomal protective protein	0.111	372
	5-lipoxygenase activating protein	0.111	310
	Integrin alpha-V/beta-3	0.111	296
	Type-1 angiotensin II receptor (by homology)	0.111	284
	Integrin alpha-4/beta-7	0.111	254
	Matrix metalloproteinase 3	0.111	248
α-19	Peroxisome proliferator-activated receptor gamma	0.122	851
	Cholecystokinin B receptor	0.122	400
	Angiotensin-converting enzyme (by homology)	0.122	393
	Lysosomal protective protein	0.122	358
	Thromboxane A2 receptor	0.122	292
	Integrin alpha-V/beta-3	0.122	285
	Type-1 angiotensin II receptor (by homology)	0.122	246
	p53-binding protein Mdm-2	0.122	217
	Thromboxane-A synthase	0.122	216
	Caspase-1	0.122	213

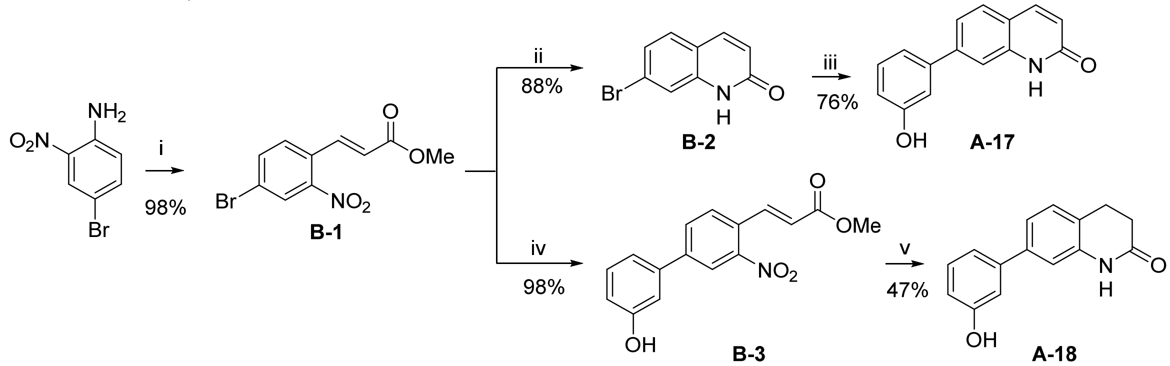
* Probability for this inhibitor to have this protein as a target.

Scheme S1. Synthesis of hydroxybiphenyls A1~16 through Suzuki coupling



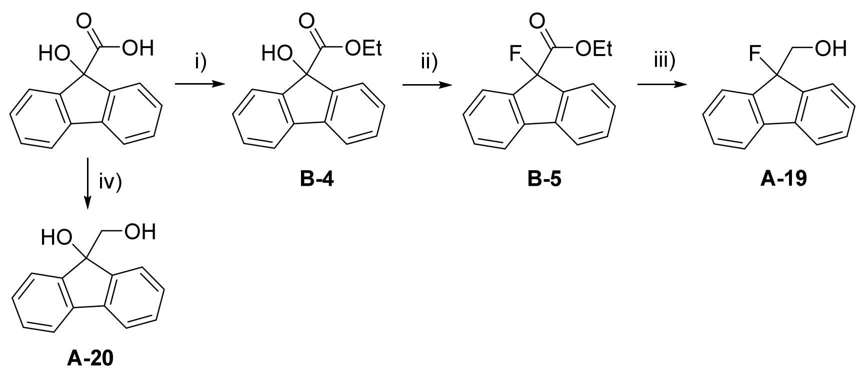


Scheme S2. Synthesis of **A-17** and **A-18**



Reagents and conditions: i) methyl acrylate, Pd(OAc)$_2$, MeSO$_3$H, ^{t}BuONO, MeOH, 0 °C to 25 °C, 65 h, ii) SnCl$_2$, Conc. HCl, EtOH, reflux, overnight, iii) 3-hydroxyphenylboronic acid, Pd(PPh$_3$)$_4$, Na$_2$CO$_3$, 1,4-dioxane/water, micowave, 125 °C, 20 min, iv) 3-hydroxyphenylboronic acid, Pd(PPh$_3$)$_4$, Na$_2$CO$_3$, 1,4-dioxane/water, reflux, 3 h, v) Pd/C, H$_2$, 50 °C, 48 h.

Scheme S3. Synthesis of **A-19** and **A-20**



Reagents and conditions: i) H_2SO_4 (cat.), ethanol, reflux, 15 h, ii) diethylaminosulfur trifluoride (DAST), dichloromethane, 0 °C to r.t., 20 h, iii) sodium borohydride, ethanol, 0 °C to r.t., 19 h, iv) borane, THF, 0 °C to r.t., 19 h.

Synthesis of hydroxybiphenyls (A1~A18), 9-fluorenemethanols (A19, A20) and their characterization data

3-(3,6-Dihydro-2*H*-pyran-4-yl)phenol (A-1). To a round-bottomed flask with a reflux condenser and a magnetic stir bar was added 3-iodophenol (189 mg, 0.86 mmol), 2-(3,6-dihydro-2*H*-pyran-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (150 mg, 0.71 mmol), and sodium carbonate (226 mg, 2.13 mmol). Then, dioxane/water (3:1, 9 mL) was added followed by N_2 gas purge for 20 min. To the mixture was added tricyclohexylphosphine (20 mg, 0.071 mmol) and $Pd_2(dba)_3$ (16.5 mg, 0.018 mmol) under nitrogen and heated under reflux overnight with stirring. The reaction mixture was diluted with ethyl acetate and water (10 mL each), and extracted with ethyl acetate (10 mL x 3). The combined organic layer was washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The resulting crude product was purified by flash column chromatography on silica gel, using 33% ethyl acetate in hexane as eluant, to afford the title compound **A-1** (100 mg, 80% yield) as a white solid: m.p. 145-147 °C; ^{1}H NMR (500 MHz, acetone-d$_6$) δ 2.46 (dt, *J* = 6.9, 2.6 Hz, 2H), 3.85 (t, *J* = 5.5 Hz, 2H), 4.24 (dd, *J* = 5.3, 2.6 Hz, 2H), 6.12 - 6.21 (m, 1H), 6.76 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.94 (dd, *J* = 8.9, 5.0 Hz, 2H), 7.17 (t, *J* = 7.9 Hz, 1H), 8.26 (s, 1H); ^{13}C NMR (126 MHz, acetone-d$_6$) δ 26.9, 63.95, 65.32, 111.52, 114.12, 115.87, 122.57, 129.31, 133.86, 141.89, 157.51; HRMS (ESI-TOF) *m/z* calcd. for $C_{11}H_{13}O_2^+$ [M+H]$^+$: 177.0910. Found 177.0910 (Δ = 0.56 ppm).

In a manner similar to that of **A-1**, **A-8** and **A-15** were synthesized and characterized.

6-(Pyrimidin-5-yl)naphthalen-2-ol (A-8). Beige solid; 28% yield; m.p. >230 °C; ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 9.94 (s, 1H), 9.25 (s, 2H), 9.18 (s, 1H), 8.29 (s, 1H), 7.87 (d, 1H, *J* = 8.8 Hz), 7.85 (s, 2H), 7.19 (d, 1H, *J* = 2.2 Hz), 7.17 (dd, 1H, *J* = 8.8, 2.2 Hz); ^{13}C NMR (500 MHz, DMSO-d$_6$) δ 157.3, 156.7, 155.0, 135.0, 133.8, 130.5, 128.3, 128.2, 127.7, 126.5, 125.0, 119.9, 109.0; HRMS (ESI-TOF) *m/z* calcd. for $C_{14}H_9NO_2^-$ [M-H]$^-$: 221.0720. Found 221.0722 (Δ = 0.9 ppm).

5-(3-Hydroxyphenyl)indolin-2-one (A-15). Yellow solid; 97% yield; m.p. >230 °C; ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 3.50 (s, 2H), 6.75 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.95 (m, 2H), 7.00 (d, *J* = 7.7 Hz, 1H), 7.14 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.32 - 7.20 (m, 2H), 9.51 (s, 1H), 10.43 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d$_6$) δ 35.6, 107.2, 113.4, 114.4, 117.3, 119.6, 124.7, 125.1, 129.9, 139.9, 141.8, 144.4, 157.8, 176.5; HRMS (ESI-TOF) *m/z* calcd. for $C_{14}H_{12}NO_2^+$ [M+H]$^+$: 226.0863. Found 226.0858 (Δ = 2.22 ppm).

In a manner similar to that of **A-1**, except for using $Pd(PPh_3)_4$ as the catalyst, **A-2**, **A-3**, **A-6**, **A-9, A-10, A-12, A-13**, **A-14**, **A-16,** were synthesized and characterized.

4-(3,6-Dihydro-2*H*-pyran-4-yl)-2-hydroxybenzonitrile (A-2). Beige solid; 70% yield: m.p. 154-155 °C; ^{1}H NMR (700 MHz, acetone-d$_6$) δ 2.47 (dd, *J* = 2.5, 1.3 Hz, 2H), 3.83 - 3.89 (m, 2H), 4.23 - 4.30 (m, 2H), 6.35 - 6.40 (m, 1H), 7.10 - 7.16 (m, 2H), 7.56 (dd, *J* = 8.0, 1.3 Hz, 1H), 9.74 (s, 1H); ^{13}C NMR (176 MHz, acetone-d$_6$) δ 26.5, 63.74, 65.27, 98.32, 111.97, 116.33, 116.63, 126.13, 132.74, 133.18, 146.40, 159.78; HRMS (ESI-TOF) *m/z* calcd. for $C_{12}H_{12}NO_2^+$ [M+H]$^+$: 202.0863. Found 202.0858 (Δ = 2.47 ppm).

3-(Benzo[*d*][1,3]dioxol-5-yl)phenol (A-3). Colorless oil; 91% yield; ^{1}H NMR (500 MHz, acetone-d$_6$) δ 6.05 (s, 2H), 6.81 (dd, *J* = 7.4, 1.7 Hz, 1H), 6.93 (dd, *J* = 8.4, 3.2 Hz, 1H), 7.06 (d, *J* = 6.8 Hz, 2H), 7.11 (dd, *J* = 3.9, 2.3 Hz, 2H), 7.25 (t, *J* = 7.9 Hz, 1H), 8.38 (s, 1H); ^{13}C NMR (126 MHz, acetone-d$_6$) δ 101.28, 107.15, 108.37, 113.54, 113.90, 117.92, 120.31, 129.78, 135.39, 142.25, 147.25, 148.29, 157.78; HRMS (ESI-TOF) *m/z* cald. for $C_{13}H_{11}O_3^+$ $[M+H]^+$: 215.0703. Found 215.0706 (Δ = 1.4 ppm).

3-(2,3-Dihydrobenzo[*b*][1,4]dioxin-5-yl)phenol (A-6). Colorless oil; >99% yield; ^{1}H NMR (500 MHz, CDCl$_3$) δ 4.30 (s, 8H), 6.86 (d, *J* = 8.3 Hz, 2H), 6.91 (t, *J* = 7.5 Hz, 2H), 6.96 (d, *J* = 8.1 Hz, 2H), 7.05 (dd, *J* = 8.3, 2.0 Hz, 2H), 7.11 (d, *J* = 2.0 Hz, 2H), 7.12 - 7.21 (m, 2H), 7.27 (dd, *J* = 7.6, 1.3 Hz, 2H), 8.20 (s, 1H); ^{13}C NMR (500 MHz, CDCl$_3$) δ 64.2, 64.4, 114.2, 116.5, 116.8, 121.0, 122.0, 122.8, 129.3, 130.4, 139.3, 140.7, 143.9, 155.2; HRMS (ESI-TOF) m/z calcd. for $C_{14}H_{13}O_3^+$ $[M+H]^+$: 229.0859. Found 229.0856 (Δ = -1.3 ppm).

4'-Fluoro-[1,1'-biphenyl]-3-ol (A-9). Yellow solid; 47% yield; m.p. 115-117 °C; ^{1}H NMR (500 MHz, CDCl$_3$) δ ppm 6.86 (dd, *J* = 7.93, 2.44 Hz, 1 H) 7.02 - 7.09 (m, 1 H) 7.10 - 7.16 (m, 3 H) 7.26 - 7.34 (m, 1 H) 7.50 - 7.56 (m, 2 H); ^{13}C NMR (500 MHz, acetone-d$_6$) δ 123.2, 124.1, 130.6, 140.8, 151.0; FIA-MS (ESI-TOF) m/z calcd. for $C_{12}H_{10}FO^+$ $[M+H]^+$: 189.1. Found 189.0. The analytical data were consistent with literature values except m.p. (lit. 76-77 ºC).[1]

3-Hydroxy-[1,1'-biphenyl]-4-carbonitrile (A-10). White solid; 92% yield; m.p. 175-177 °C (lit.[1] 180-181 ºC); ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 7.20 - 7.28 (m, 2 H) 7.39 - 7.45 (m, 1 H) 7.45 - 7.56 (m, 3 H) 7.60 - 7.76 (m, 3 H) 11.23 (s, 1 H); ^{13}C NMR (500 MHz, DMSO-d$_6$) δ ppm 98.3, 114.5, 117.5, 118.7, 127.4, 129.2, 134.2, 139.1, 146.9, 161.0; HRMS (ESI-TOF) m/z calcd. for $C_{13}H_{10}NO^+$ $[M+H]^+$: 196.0757. Found 196.0760 (Δ = -1.53 ppm). The analytical data were consistent with literature values.[1]

4-(2'-Hydroxyphenyl)benzenecarbonitrile (A-12). White solid; 58% yield; m.p. 119-120 °C (lit.[2] 119-120 ºC); ^{1}H NMR (500 MHz, acetone-d$_6$) δ 8.67 (s, 1H), 7.86 - 7.77 (m, 4H), 7.37 (d, *J* = 5.9 Hz, 1H), 7.26 (t, *J* = 7.7 Hz, 1H), 7.03 (d, *J* = 9.6 Hz, 1H), 6.98 (t, *J* = 8.1 Hz, 1H); ^{13}C NMR (176 MHz, acetone-d$_6$) δ 155.18, 144.60, 132.60, 131.38, 131.03, 130.69, 127.37, 121.16, 119.58, 117.21, 117.09, 110.97; FIA-MS (ESI-TOF) *m/z* calcd. for $C_{13}H_8NO^-$ $[M-H]^-$: 194.1. Found 194.0. The analytical data were consistent with literature values.[2]

6-(3-Hydroxyphenyl)indolin-2-one (A-13). Yellow solid; 74% yield; m.p. >230 °C; ^{1}H NMR (300 MHz, acetone-d6) δ 3.49 (s, 2H), 6.75 (dd, *J* = 8.0, 1.6, 1H), 6.95 (d, *J* = 4.0, 2H), 7.00 (d, *J* = 7.8, 1H), 7.14 (dd, *J* = 7.7, 1.6, 1H), 7.24 (dd, *J* = 15.0, 7.4, 2H), 8.44 (s, 1H), 9.43 (s, 1H); ^{13}C NMR (126 MHz, DMSO-d$_6$) δ 35.6, 107.2, 113.4, 114.4, 117.3, 119.6, 124.7, 125.1, 129.9, 140.0, 141.8, 144.4, 157.8, 176.5; HRMS (ESI-TOF) calcd. for $C_{14}H_{12}NO_2^+$ $[M+H]^+$: 226.0863. Found 226.0859 (Δ = 1.77 ppm).

6-(2-Hydroxyphenyl)indolin-2-one (A-14). Beige solid; 28% yield for three steps; m.p. 192-193 °C; ^{1}H NMR (700 MHz, acetone-d$_6$) δ 3.49 (s, 1H), 6.93 (t, *J* = 7.4 Hz, 1H), 6.99 (d, *J* = 8.1 Hz, 1H), 7.16 (d, *J* = 6.1 Hz, 2H), 7.17 - 7.21 (m, 1H), 7.26 - 7.31 (m, 2H), 8.29 (s, 1H), 9.39 (s, 1H); ^{13}C NMR (176 MHz, acetone-d$_6$) δ 35.32, 110.36, 116.10, 119.93, 122.44, 124.10, 124.12, 124.30, 128.48, 130.47, 138.42, 143.52, 154.11, 175.99; HRMS (ESI-TOF) *m/z* calcd. for $C_{14}H_{12}NO_2^+$ $[M+H]^+$: 226.0863. Found = 226.0861 (Δ = 0.88 ppm).

6-(3-Hydroxyphenyl)-3,4-dihydroquinolin-2(1*H*)-one (A-16). White solid; 33% yield; m.p. >230 °C; ^{1}H NMR (700 MHz, acetone-d$_6$) δ 2.56 (t, *J* = 7.5 Hz, 2H), 3.04 (t, *J* = 7.5 Hz, 2H), 6.82 (d, *J* = 8.2 Hz, 1H), 7.02 (d, *J* = 8.1 Hz, 1H), 7.11 (d, *J* = 7.7 Hz, 2H), 7.26 (t, *J* = 7.8 Hz, 1H), 7.44 (d, *J* = 8.1 Hz, 1H), 7.47 (s,1H), 8.38 (s, 1H), 9.15 (s, 1H); ^{13}C NMR (176 MHz, DMSO-d$_6$) δ 25.3, 30.88, 113.48, 114.36, 115.86, 117.38, 124.45, 125.72, 126.42, 130.27, 134.52, 138.21, 141.79, 158.30, 170.67; HRMS (ESI-TOF) *m/z* calcd. for $C_{15}H_{14}NO_2^+$ $[M+H]^+$: 240.1019. Found = 240.1020 (Δ = 0.22 ppm).

In a manner similar to that of **A-1**, except for using $Pd(PPh_3)_2Cl_2$ as the catalyst and LiOH as the base, **A-5** was synthesized and characterized.

3-(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)phenol (A-5). Colorless oil; 95% yield; ^{1}H NMR (500 MHz, acetone-d$_6$) δ 4.31 (d, *J* = 3.9 Hz, 4H), 6.83 - 6.77 (m, 1H), 6.90 (dd, *J* = 8.1, 3.6 Hz, 1H), 7.12 - 7.02 (m, 4H), 7.25 (t, *J* = 7.6 Hz, 1H), 8.35 (s, 1H); ^{13}C NMR (126 MHz, acetone-d$_6$) δ 64.35, 64.37, 113.32, 113.82, 115.32, 117.38, 117.72, 119.60, 129.76, 134.37, 141.98, 143.47, 143.93, 157.79; HRMS (ESI-TOF) *m/z* calcd. for $C_{14}H_{13}O_3^+$ $[M+H]^+$: 229.0859. Found 229.0853 (Δ = 2.63 ppm).

In a manner similar to that of **A-1**, except for using $Pd(PPh_3)_2Cl_2$ as the catalyst and K_2CO_3 as the base, **A-4, A-7** and **A-11**were synthesized and characterized.

2-(Benzo[*d*][1,3]dioxol-5-yl)phenol (A-4). White solid; 58% yield; m.p. 81-83 °C (lit.[3] 88-90 ºC); ^{1}H NMR (500 MHz, acetone-d$_6$) δ 4.17 (dd, *J* = 10.7, 7.3, 1H), 4.38 (dd, *J* = 10.7, 7.3, 1H), 4.64 (dd, *J* = 10.7, 7, 1H), 4.71 (dd, *J* = 10.7, 7.3, 1H), 6.69 (dd, *J* = 8.9, 2.1, 1H), 6.96 (s, 1H), 7.29 (m, 1H), 7.39 (t, *J* = 7.5, 7.5, 2H), 7.5 (m, 5H), 7.62 (d, *J* = 7.3, 2H), 7.91 (m, 3H), 8.32 (s, 1H), 9.19 (m, 3H); ^{13}C NMR (500 MHz, acetone-d$_6$) δ 41.3, 46.8, 118.4, 126.2, 126.9, 127.3, 127.8, 128.2, 128.6, 129.5, 131.5, 131.6, 154.9, 157.9, 170.6; FIA-MS (ESI-TOF) m/z calcd. for $C_{13}H_{11}O_3^+$ $[M+H]^+$: 215.1. Found 215.0. The analytical data were consistent with literature values.[3]

2-(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)phenol (A-7). Beige solid; 70% yield; m.p. 115-117 °C; ^{1}H NMR (500 MHz, acetone-d$_6$) δ ppm 4.26 (d, *J* = 4.5 Hz, 2H), 4.29 (d, *J* = 4.6 Hz, 2H), 6.83 (dd, *J* = 9.1, 6.0 Hz, 2H), 6.87 (d, *J* = 4.0 Hz, 2H), 6.99 (d, *J* = 7.6 Hz, 1H), 7.04 (s, 1H), 7.23 (t, *J* = 7.9 Hz, 1H), 8.31 (s, 1H); ^{13}C NMR (500 MHz, acetone-d$_6$) δ 64.0, 64.17, 113.88, 116.35, 116.42, 120.61, 120.75, 122.30, 128.85, 130.82, 139.29, 140.91, 144.16, 156.95; HRMS (ESI-TOF) m/z calculated for $C_{14}H_{13}O_3^+$ $[M+H]^+$: 229.0859. Found 229.0867, (Δ = -3.22 ppm).

3'-Hydroxy-[1,1'-biphenyl]-4-carbonitrile (A-11). White solid; 81% yield; m.p. 155-156 °C (lit.[4] 148-150 ºC); ^{1}H NMR (500 MHz, acetone-d$_6$) δ 6.98 - 6.91 (m, 1H), 7.24 - 7.15 (m, 2H), 7.36 (t, *J* = 7.9 Hz, 1H), 7.88 - 7.81 (m, 4H), 8.60 (s, 1H); ^{13}C NMR (126 MHz, acetone-d$_6$) δ 110.87, 113.96, 115.66, 118.38, 118.49, 127.70, 130.25, 132.61, 140.51, 145.42, 158.06; HRMS (ESI-TOF) m/z calculated for $C_{13}H_8NO^-$ $[M-H]^-$: 194.0611. Found 194.0611, (Δ = 0 ppm). The analytical data were consistent with literature values[4].

Methyl (*E*)-3-(4-bromo-2-nitrophenyl)acrylate (B-1). This compound was prepared by the literature method[6]. Yellow solid; 98% yield; m.p. 84-85 °C (lit.[6] 84-85 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.22 (s, 1H), 8.06 (d, *J* = 15.8 Hz, 1H), 7.80 (d, *J* = 8.3 Hz, 1H), 7.54 (d, *J* = 8.3 Hz, 1H), 6.39 (d, *J* = 15.8 Hz, 1H), 3.86 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.98, 148.55, 138.99, 136.62, 130.29, 129.40, 128.01, 123.80, 123.43, 52.15; FIA-MS (ESI-TOF) *m/z* calcd. for $C_{10}H_9BrNO_4^+$ $[M+H]^+$: 286.0. Found 285.9. The analytical data were consistent with literature values.[6]

7-Bromoquinolin-2(1*H*)-one (B-2). To a round-bottomed flask with a reflux condenser and a magnetic stir bar was added tin (II) chloride (1.82 mg, 8.10 mmol), ethanol (5 mL), and concentrated HCl (1 mL). The mixture was stirred and heated to 70 °C until it became a clear solution. To this refluxing solution was added methyl (*E*)-3-(4-bromo-2-nitrophenyl)acrylate (575 mg, 2.04 mmol) (**B-1**). The mixture was heated under reflux overnight with stirring. To the reaction mixture was added water (5 mL) and allowed to cool down to 5 °C. The mixture was stirred at 5 °C for 30 min. The precipitate was collected via vacuum filtration, washed with water (5 mL), and dried *in vacuo* to afford the title compound **B-2** (380 mg, 88% yield) as a white solid: m.p. >230 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.81 (s, 1H), 7.90 (d, *J* = 9.6 Hz, 1H), 7.62 (d, *J* = 8.4 Hz, 1H), 7.48 (d, *J* = 1.6 Hz, 1H), 7.34 (dd, *J* = 8.4, 1.8 Hz, 1H), 6.53 (d, *J* = 9.6 Hz, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 162.15, 140.43, 140.25, 130.27, 125.12, 123.88, 122.88, 118.65, 117.82; FIA-MS (ESI-TOF) *m/z* calcd. for $C_9H_7BrNO^+$ $[M+H]^+$: 224.0. Found 224.0. The analytical data were consistent with literature values.[7]

7-(3-Hydroxyphenyl)quinolin-2(1*H*)-one (A-17). To a microwave vial with a magnetic stir bar was added 3-hydroxyphenylboronic acid (220 mg, 1.57 mmol), 7-bromoquinolin-2(1*H*)-one (**B-2**) (200 mg, 0.90 mmol), potassium carbonate (190 mg, 1.8 mmol), and $Pd(PPh_3)_4$ (100 mg, 0.09 mmol). Then, dioxane/water (3:1, 9 mL) was added to the mixture, followed by N_2 gas purge for 20 min. The mixture was reacted in a microwave reactor (125 °C, 300 W) for 20 min. To the reaction mixture was added water (20 mL) and allowed to cool down to 5 °C. The precipitate was collected via vacuum filtration, washed with cold dichloromethane (25 mL), and dried *in vacuo* to afford the title compound **A-17** (160 mg, 76% yield) as a white solid: m.p. >220 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.49 (d, *J* = 9.8 Hz, 1H), 6.82 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.15 - 6.97 (m, 2H), 7.30 (t, *J* = 7.9 Hz, 1H), 7.41 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.49 (s, 1H), 7.72 (d, *J* = 8.2 Hz, 1H), 7.93 (d, *J* = 9.5 Hz, 1H), 9.64 (s, 1H), 11.79 (s, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 113.17, 114.06, 115.64, 118.10, 118.89, 121.03, 122.26, 128.89, 130.63, 139.80, 140.36, 141.26, 142.70, 158.38, 162.53; HRMS (ESI-TOF) *m/z* calc. for $C_{15}H_{12}NO_2^+$ $[M+H]^+$: 238.0863. Found 238.0861 (Δ = 0.84 ppm).

Methyl (*E*)-3-(3'-hydroxy-3-nitro-[1,1'-biphenyl]-4-yl)acrylate (B-3). To a round-bottomed flask with a reflux condenser and magnetic stir bar was added methyl (*E*)-3-(4-bromo-2-nitrophenyl)acrylate (410 mg, 1.43 mmol), 3-hydroxyphenyl boronic acid (290 mg, 2.14 mmol), and sodium carbonate (450 mg, 4.28 mmol). Then, dioxane/water (4:1, 20 mL) was added to the mixture, followed by N_2 gas purge for 20 min. To the mixture was added tetrakis(triphenylphosphine)palladium(0) (160 mg, 0.14 mmol) under nitrogen and heated under reflux for 3 h with stirring. The reaction mixture was diluted with ethyl acetate and water (20 mL each), and extracted with ethyl acetate (20 mL x 2). The combined organic layer was washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The resulting crude product was purified by flash column chromatography on silica gel, using 25% ethyl acetate in hexane as eluant, to afford the title compound **B-3** (420 mg, 98% yield) as a yellow solid: m.p. 137-140 °C; ^{1}H NMR (500 MHz, acetone-d$_6$): δ 3.83 (s, 3H), 6.33 - 6.41 (m, 1H), 6.64 (d, *J* = 15.8 Hz, 1H), 6.97 - 7.03 (m, 1H), 7.26 - 7.31 (m, 2H), 7.39 (t, J = 7.9 Hz, 1H), 8.01 - 8.12 (m, 3H), 8.30 (s, 1H); ^{13}C NMR (125 MHz, acetone-d$_6$): δ 51.5, 106.96, 114.12, 116.30, 118.54, 122.64, 122.89, 128.52, 129.93, 130.73, 131.72, 139.33, 143.74, 149.70, 158.49, 166.25; HRMS (ESI-TOF) *m/z* calculated for $C_{16}H_{13}NNaO_5^+$ [M+Na]$^+$: 322.0686. Found = 322.0691 (Δ = 1.56 ppm).

7-(3-Hydroxyphenyl)-3,4-dihydroquinolin-2(1*H*)-one (A-18). To a round-bottomed flask with a magnetic stir bar was added methyl (*E*)-3-(3'-hydroxy-3-nitro-[1,1'-biphenyl]-4-yl)acrylate (**B-3**) (420 mg, 1.40 mmol), 10% Pd/C (70 mg, 0.66 mmol), and methanol (14 mL). The atmosphere of the reaction flask was exchanged with H_2 for 3 times and the reaction was heated to 40 °C for 24 h with stirring. The reaction mixture was filtered through celite and concentrated in *vacuo*. The crude product, thus obtained, was purified by flash column chromatography on silica gel, using gradient of ethyl acetate in hexanes from 50% to 80%, to afford the title compound **A-18** (160 mg, 47% yield) as a white solid: m.p. 230 °C (decomp.); ^{1}H NMR (500 MHz, acetone-d$_6$): δ 2.53 (d, *J* = 7.5 Hz, 2H), 2.98 (t, *J* = 7.5 Hz, 2H), 6.83 (d, *J* = 8.0 Hz, 1H), 7.03 - 7.10 (m, 2H), 7.18 (d, *J* = 6.8 Hz, 2H), 7.21 - 7.30 (m, 2H), 8.41 (s, 1H), 9.07 (s, 1H); ^{13}C NMR (500 MHz, DMSO-d$_6$): δ 24.9, 30.9, 113.5, 113.7, 114.9, 117.7, 120.7, 123.3, 128.7, 130.4, 139.2, 139.9, 141.9, 158.2, 170.7; HRMS (ESI-TOF) *m/z* calcd. for $C_{15}H_{14}NO_2$ [M+H]$^+$: 240.1019. Found 240.1020 (Δ = 0.42 ppm).

Ethyl 9-hydroxy-9*H*-fluorene-9-carboxylate (B-4). This compound was prepared by the literature method.[8] White solid; 91% yield; m.p. 92-93 °C (lit.[8] 90 °C); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.67 (d, *J* = 7.6 Hz, 2H), 7.44 (d, *J* = 7.3 Hz, 2H), 7.41 (d, *J* = 7.5 Hz, 2H), 7.30 (t, *J* = 7.5 Hz, 2H), 4.29 (s, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 1.02 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.5, 145.1, 141.0, 129.7, 128.2, 123.5, 120.4, 82.4, 62.7, 13.8; HRMS (ESI-TOF) *m/z* calculated for $C_{16}H_{18}NO_3^+$ [M+NH$_4$]$^+$: 272.1292. Found = 272.1281. (Δ = -4.0 ppm). The analytical data were consistent with literature values[8].

Ethyl 9-fluoro-9*H*-fluorene-9-carboxylate (B-5). To a solution of ethyl 9-hydroxy-9*H*-fluorene-9-carboxylate (**B-4**) (0.37 g, 1.46 mmol) in DCM (8 mL) was added diethylaminosulfur trifluoride (0.23 mL, 1.76 mmol) at 0 °C. The reaction mixture was gradually warmed to room temperature and stirred for 50 h. The reaction mixture was diluted with dichloromethane and water (20 mL each). The combined organic layer was washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The resulting crude product was purified by flash column chromatography on silica gel, using 20% ethyl acetate in hexane as eluant, to afford the title compound (0.35 g, 93% yield) as a white solid: m.p. 71-72 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.16 (t, *J* = 7.1 Hz, 3H), 4.22 (q, *J* = 7.1 Hz, 2H), 7.32 (t, *J* = 7.5 Hz, 2H), 7.46 (t, *J* = 7.5 Hz, 2H), 7.56 (d, *J* = 7.4 Hz, 2H), 7.64 (d, *J* = 7.6 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.9, 62.16, 97.66 (d, $^1J_{C,F}$ = 192.6 Hz), 120.56, 124.72, 128.45 (d, $^3J_{C,F}$ = 1.7 Hz), 130.99, 140.85 (d, $^2J_{C,F}$ = 19.0 Hz), 141.33 (d, $^3J_{C,F}$ = 2.6 Hz), 169.09 (d, $^2J_{C,F}$ = 33.4 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): δ -161.2; HRMS (ESI-TOF) *m/z* calcd. for $C_{16}H_{17}FNO_2^+$ [M+NH$_4$]$^+$: 274.1238. Found = 274.1238. (Δ = 0.0 ppm).

(9-Fluoro-9*H*-fluoren-9-yl)methanol (A-19). To a solution of ethyl 9-fluoro-9*H*-fluorene-9-carboxylate (**B-5**) (0.4 g, 1.57 mmol) in ethanol (16 mL) was added sodium borohydride (0.12 g, 3.14 mmol) at 0 °C. The reaction mixture was gradually warmed to room temperature and stirred for 19 h. The ethanol was removed *in vacuo*. The resulting crude product was purified by flash column chromatography on silica gel, using 20% ethyl acetate in hexane as eluant, to afford the title compound **A-19** (0.29 g, 86% yield) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.08 (d, $^1J_{H,F}$ = 19.3 Hz, 2H), 7.35 (t, J = 7.5 Hz, 2H), 7.47 (t, J = 7.5 Hz, 2H), 7.68 (t, J = 7.7 Hz, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 66.94 (d, $^2J_{C,F}$ = 30.6 Hz), 100.25 (d, $^1J_{C,F}$ = 181.6 Hz), 120.31, 125.14, 128.13 (d, $^3J_{C,F}$ = 1.7 Hz), 130.55, 140.46 (d, $^3J_{C,F}$ = 3.0 Hz), 141.64 (d, $^2J_{C,F}$ = 18.7 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): δ -169.69; HRMS (ESI-TOF) *m/z* calculated for $C_{14}H_{11}O^+$ $[M-F]^+$: 195.0810. Found = 195.0818. (Δ = 4.1 ppm).

(9-Hydroxy-9*H*-fluoren-9-yl)methanol (A-20). To a round-bottomed flask with a reflux condenser and a magnetic stir bar was added 9-hydroxy-9*H*-fluorene-9-carboxylic acid (1.0 g, 4.44 mmol) and THF (44 mL). To the mixture borane dimethyl sulfide (7.4 mL, 14.8 mmol, 2M in THF) was added at 0 °C. The mixture was heated under reflux overnight with stirring. The solvent was removed *in vacuo*. The resulting crude product was purified by flash column chromatography on silica gel, using gradient methanol in dichloromethane from 2% to 10%, to afford the title compound **A-20** (898 mg, 95% yield) as a white solid: m.p. 96-97 °C; (lit. 94-96 °C) ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.64 (d, J = 7.5 Hz, 2H), 7.59 (d, J = 7.4 Hz, 2H), 7.39 (t, J = 7.5 Hz, 2H), 7.30 (t, J = 7.4 Hz, 2H), 3.81 (s, 2H), 2.71 (brs, 1H), 2.47 (brs, 1H); FIA-MS (ESI-TOF) m/z calcd. for $C_{14}H_{11}O_2^-$ $[M-H]^-$: 211.1. Found 211.0. The analytical data were consistent with literature values.[9]

References

1. Zhang, W.; Yang, W.; Zhao, W., Lewis acid-promoted site-selective cyanation of phenols. *Org Biomol Chem* **2020,** *18*, 4604-4609.
2. Inamoto, K.; Kadokawa, J.; Kondo, Y., Ruthenium-Catalyzed Carbonylative C-H Cyclization of 2-Arylphenols A Novel Synthetic Route to 6H-Dibenzo[b,d]pyran-6-ones. *Org Lett* **2013,** *15* (15), 3962-3965.
3. Lee, T.-H.; Jayakumar, J.; Cheng, C.-H.; Chuang, S.-C., One pot synthesis of bioactive benzopyranones through palladium- atalyzed C–H activation and CO insertion into 2-arylphenols. *Chem Commun* **2013,** *49*, 11797-11799.
4. Moorthy, J. N.; Koner, A. L.; Samanta, S.; Roy, A.; Nau, W. M., Modulation of spectrokinetic properties of o-quinonoid reactive intermediates by electronic factors: time-resolved laser flash and steady-state photolysis investigations of photochromic 6- and 7-arylchromenes. *Chemistry* **2009,** *15* (17), 4289-300.
5. Hong, P. C.; Chen, L. J.; Lai, T. Y.; Yang, H. Y.; Chiang, S. J.; Lu, Y. Y.; Tsai, P. K.; Hsu, H. Y.; Wei, W. Y.; Liao, C. B., Synthesis of selenophene derivatives as novel CHK1 inhibitors. *Bioorg Med Chem Lett* **2010,** *20* (17), 5065-8.
6. Callonnec, F. L.; Fouquet, E.; Felpin, F. X., Unprecedented Substoichiometric Use of Hazardous Aryl Diazonium Salts in the Heck-Matsuda Reaction via a Double Catalytic Cycle. *Org Lett* **2011,** *13* (10), 2646-2649.
7. Alabaster, C. T.; Bell, A. S.; Campbell, S. F.; Ellis, P.; Henderson, C. G.; Roberts, D. A.; Ruddock, K. S.; Samuels, G. M. R.; Stefaniak, M. H., 2(1H)-Quinolinones with cardiac stimulant activity. 1. Synthesis and biological activities of (six-membered heteroaryl)-substituted derivatives. *J. Med. Chem.* **1988,** *31* (10), 2048-2056.
8. Galvez, E.; Trigo, G. G.; Martinez, M.; Cabezas, N., Synthesis and structural study of cyclopentane, indene and fluorene spiro-derivatives. *J. Heterocycl. Chem.* **1983,** *20* (1), 13-16.
9. Mladenove, G.; Singh, G.; Acton, A.; Chen, L.; Rinco, O.; Johnston, L. J.; Lee-Ruff, E., Photochemical Pinacol Rearrangements of Unsymmetrical Diols. *J Org Chem* **2004,** *69* (6), 2017-2023.

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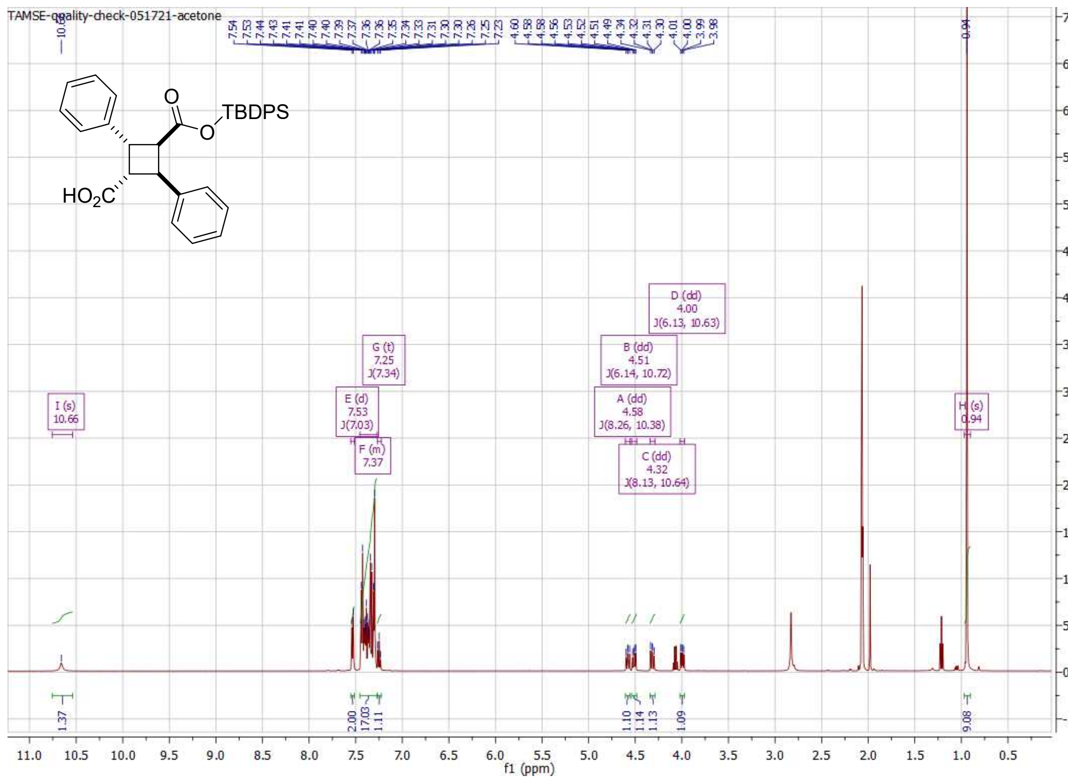

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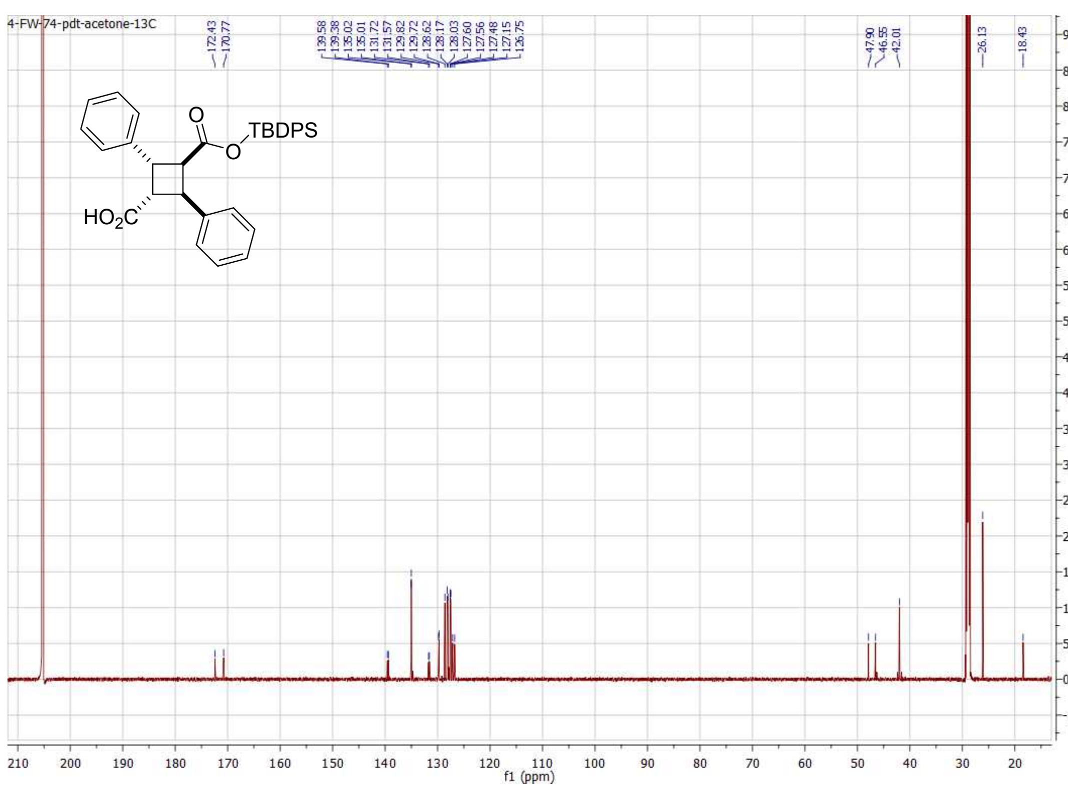

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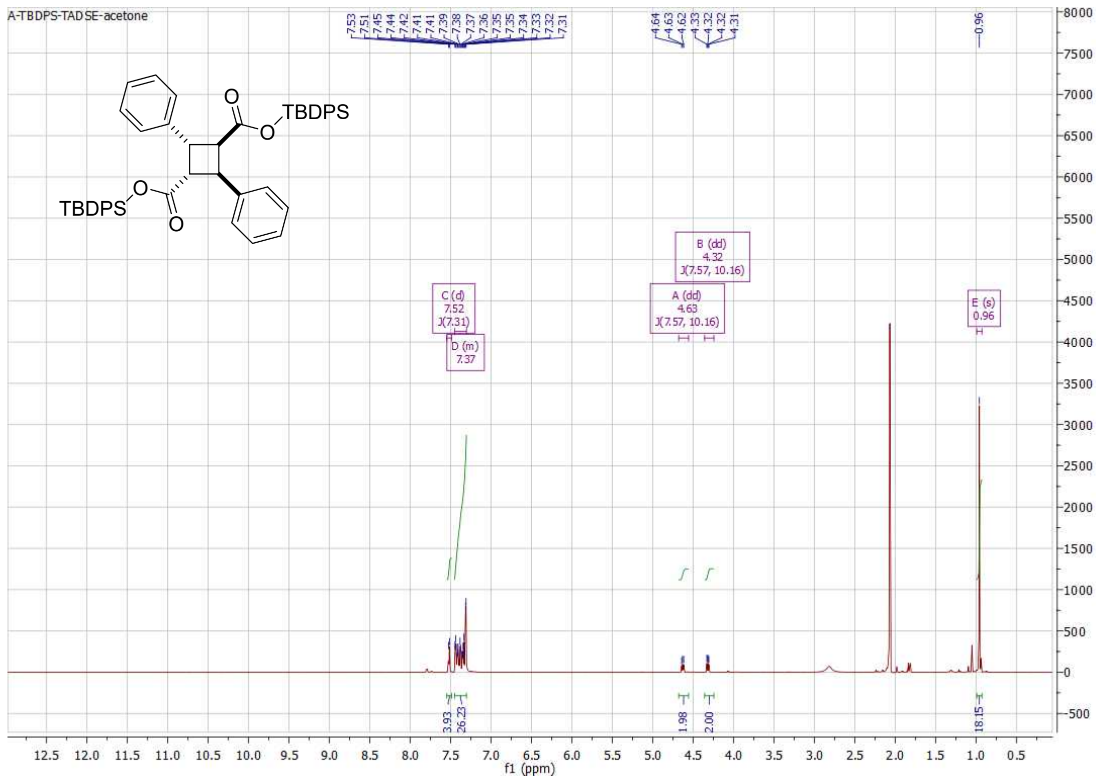

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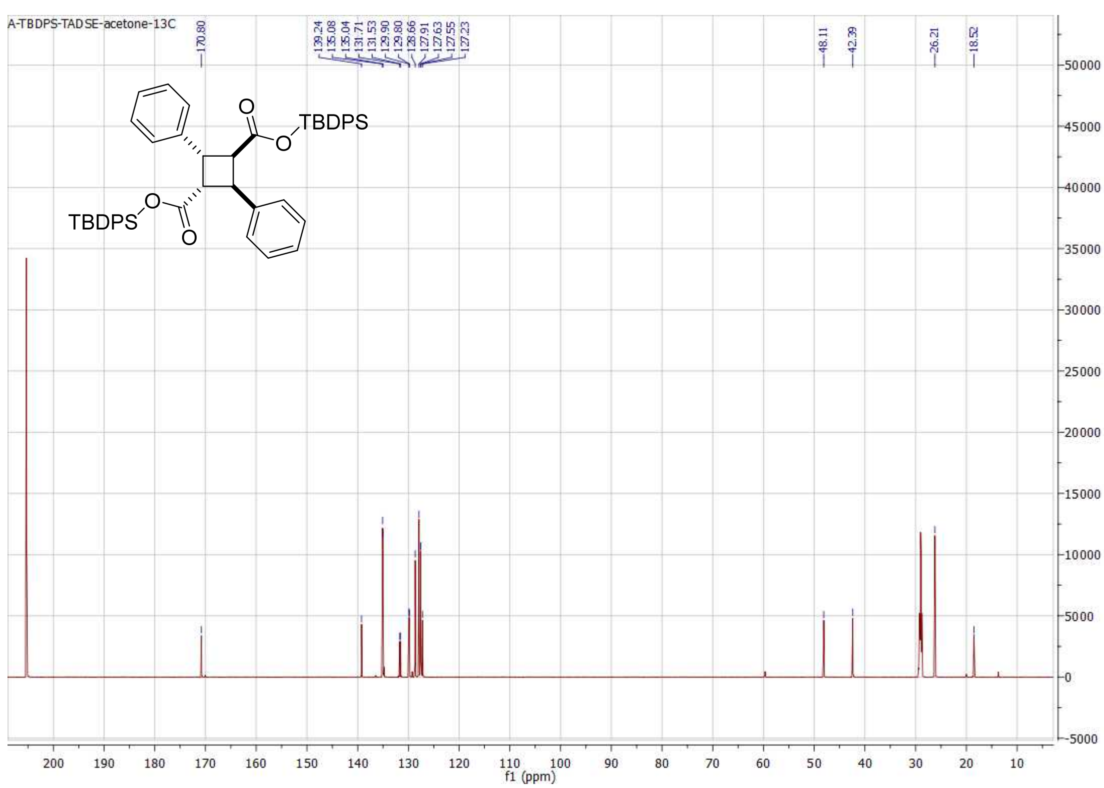

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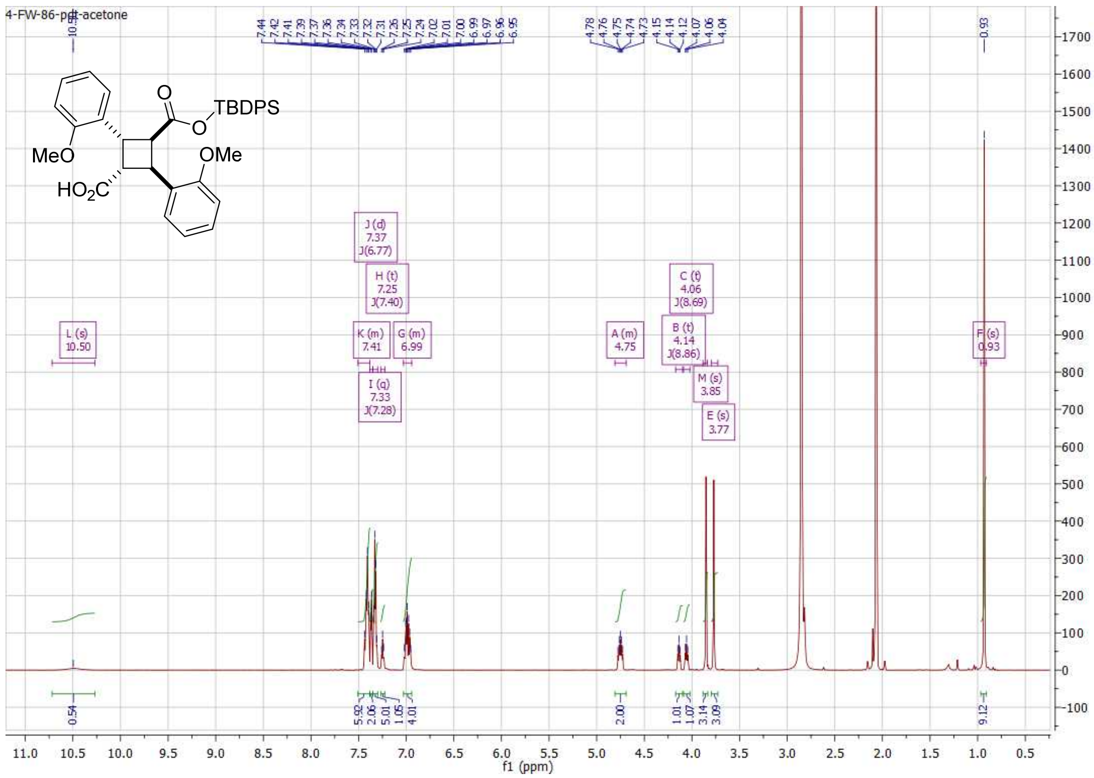

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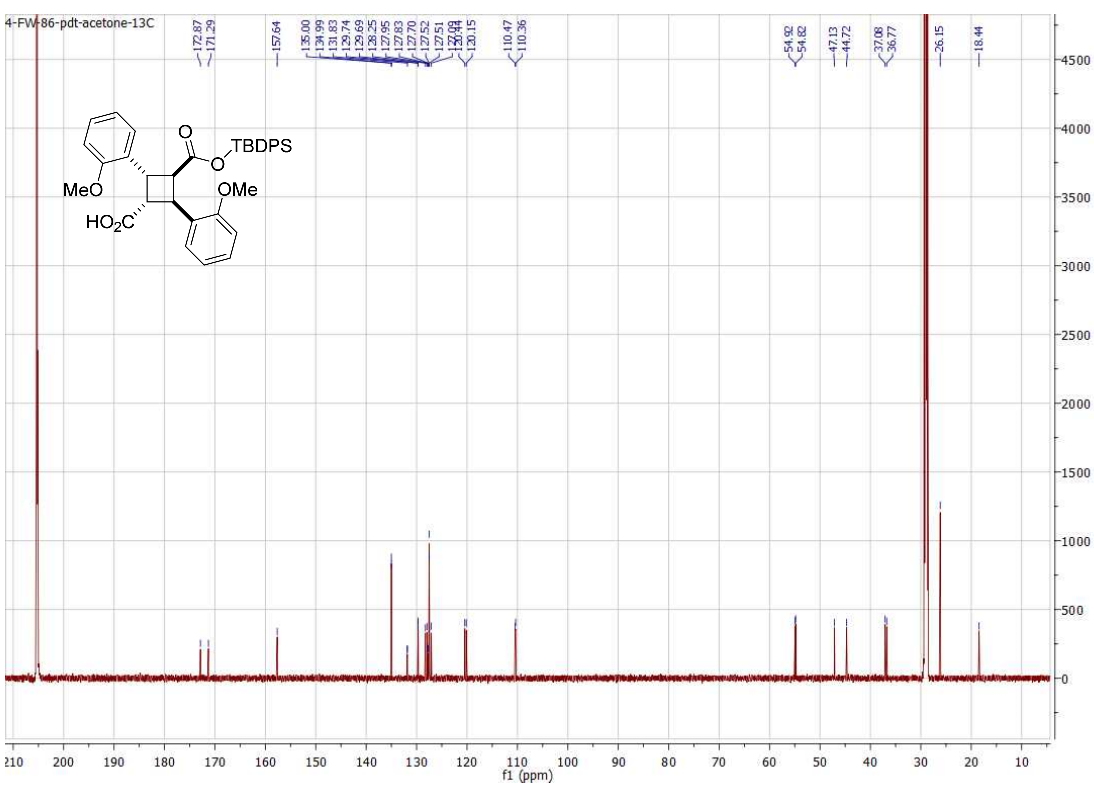

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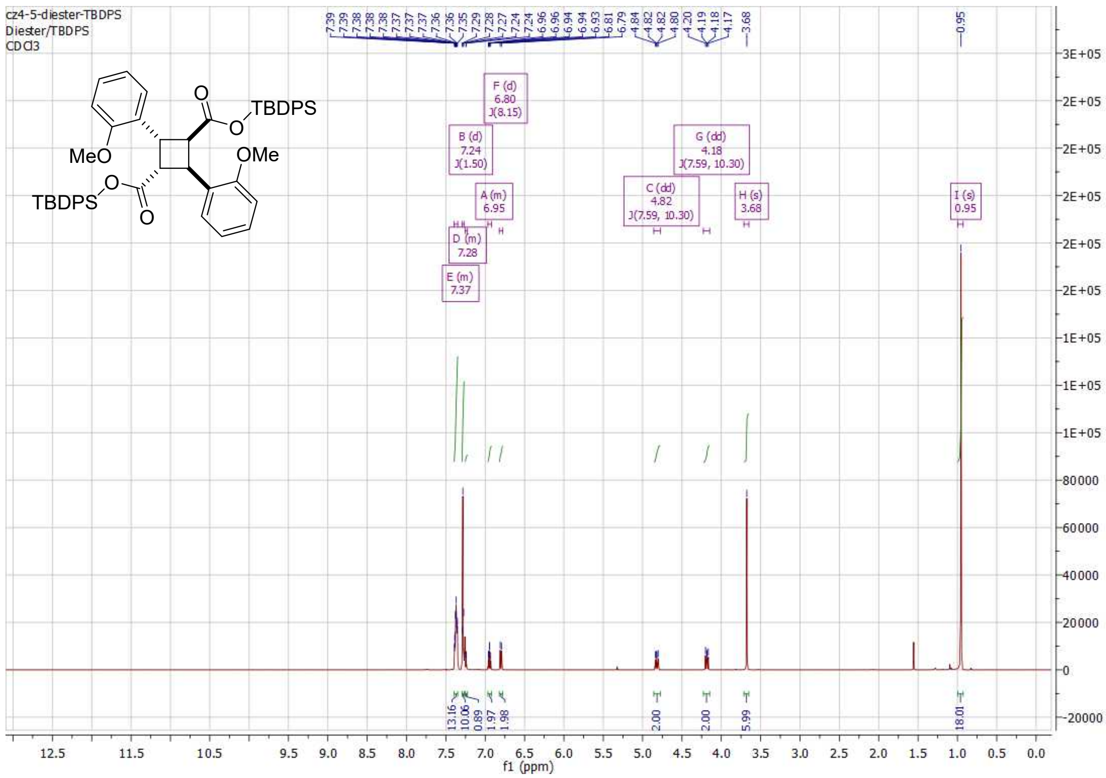

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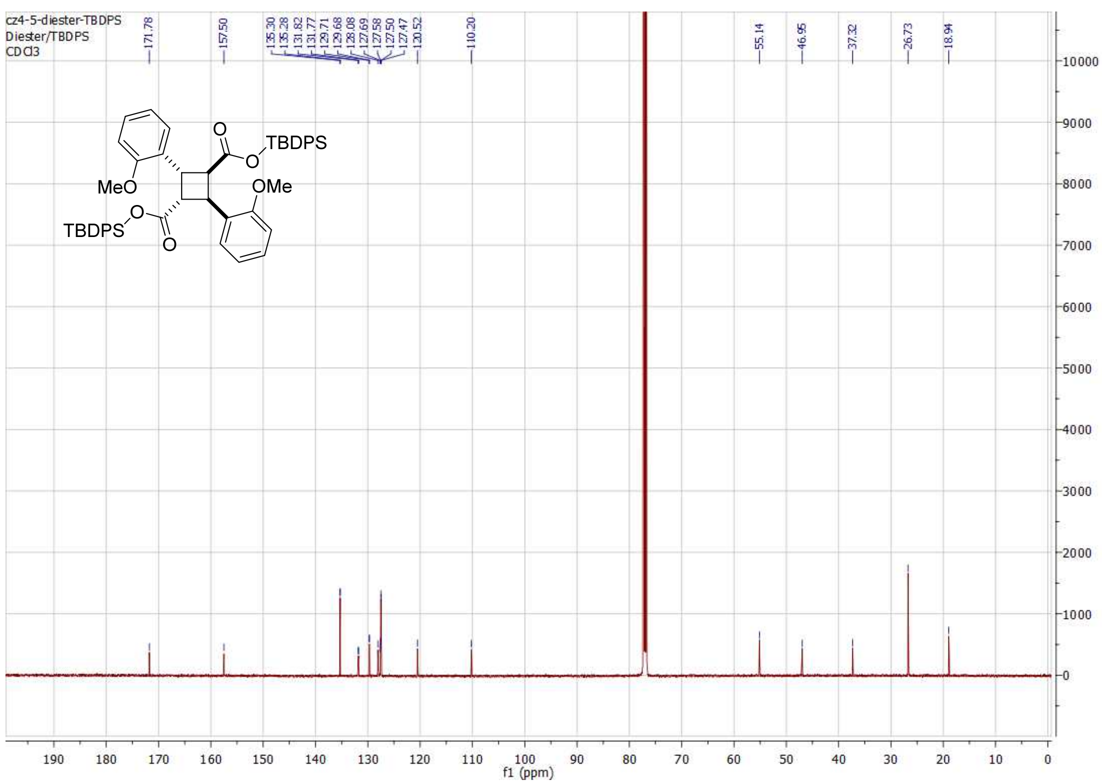

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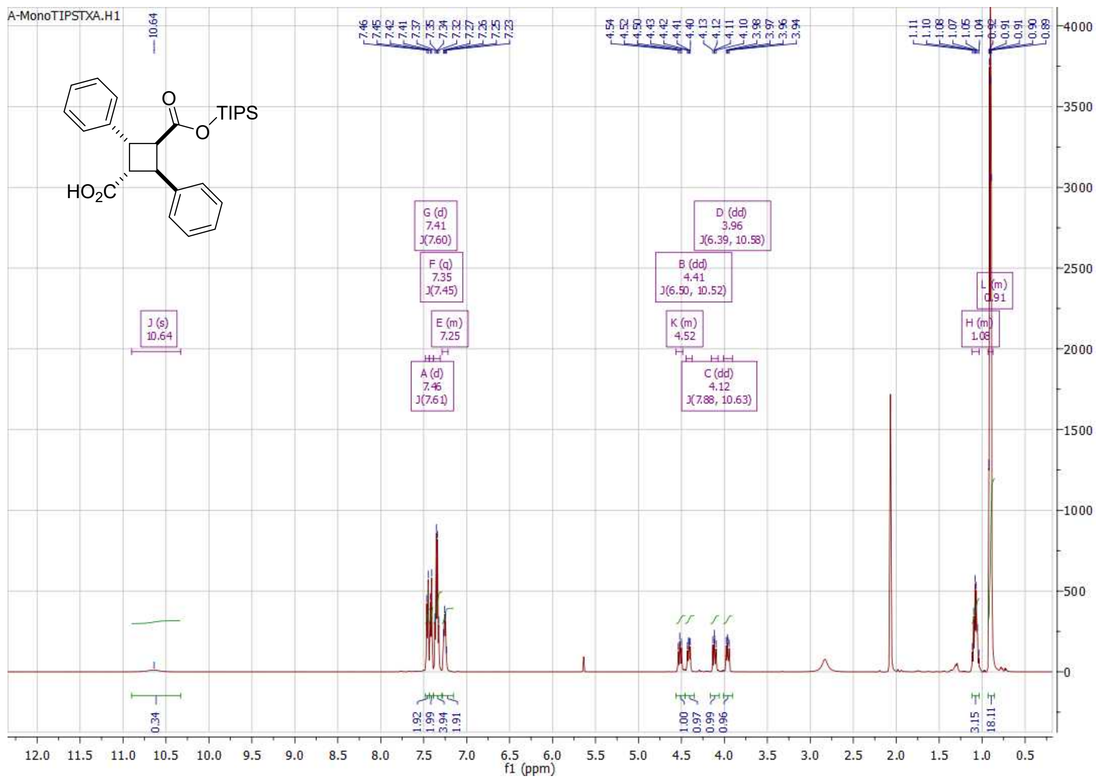

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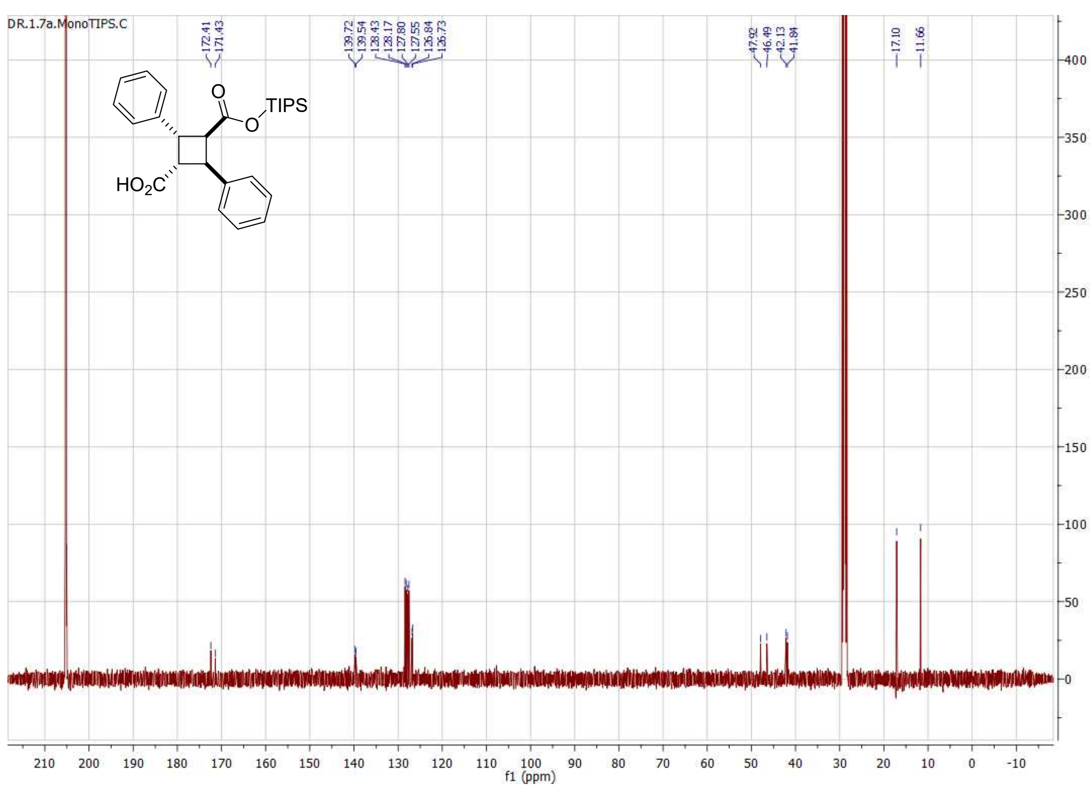

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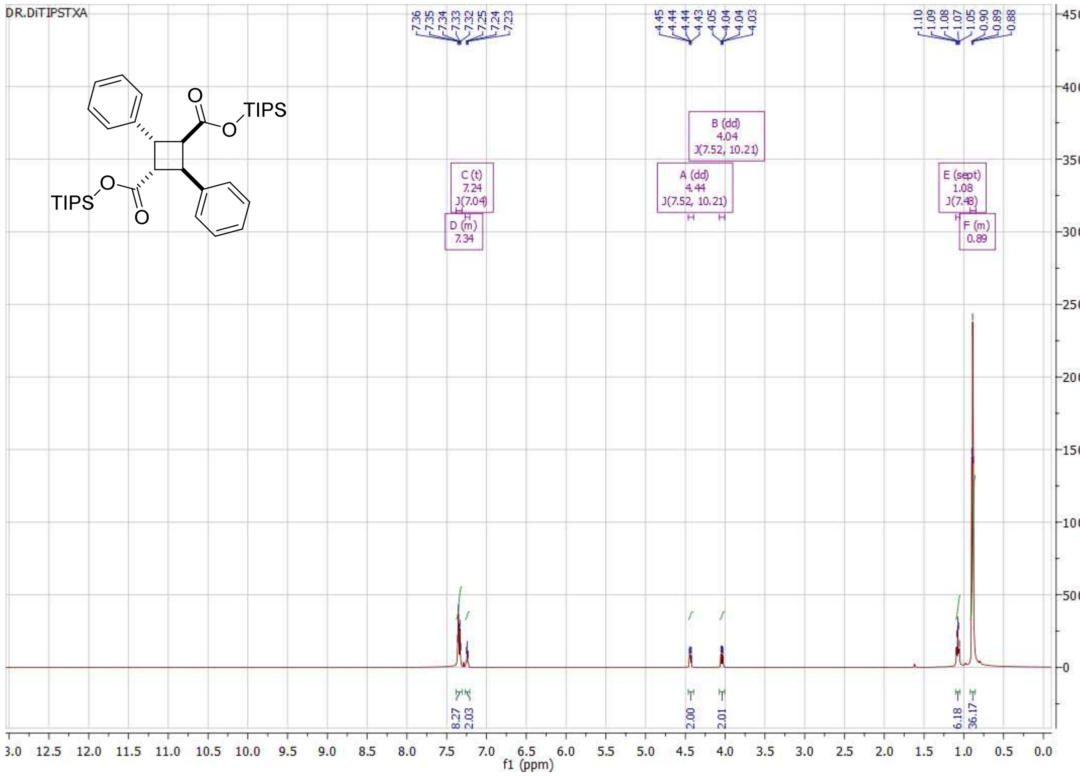

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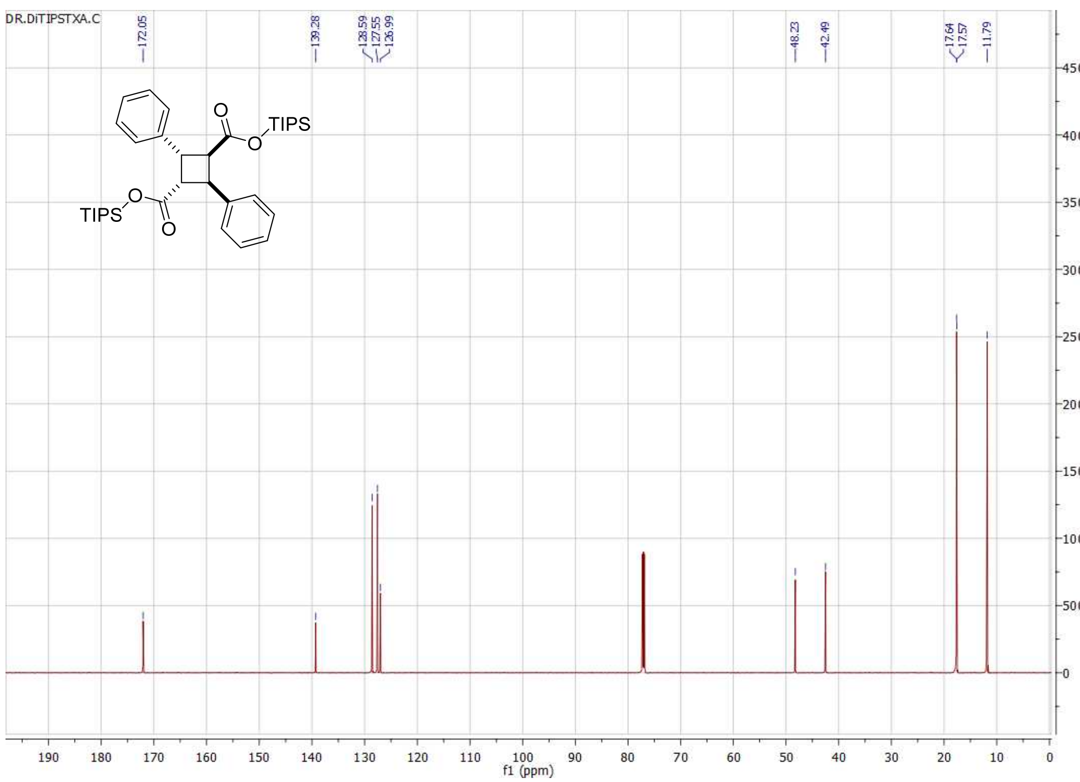

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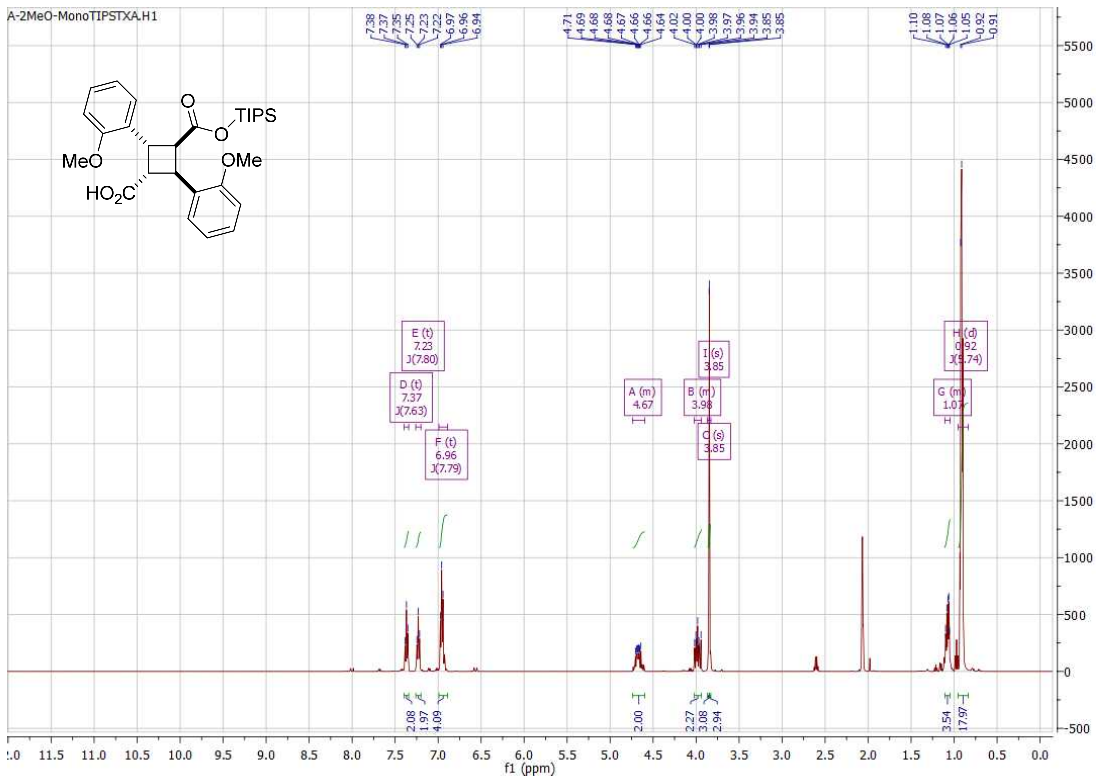

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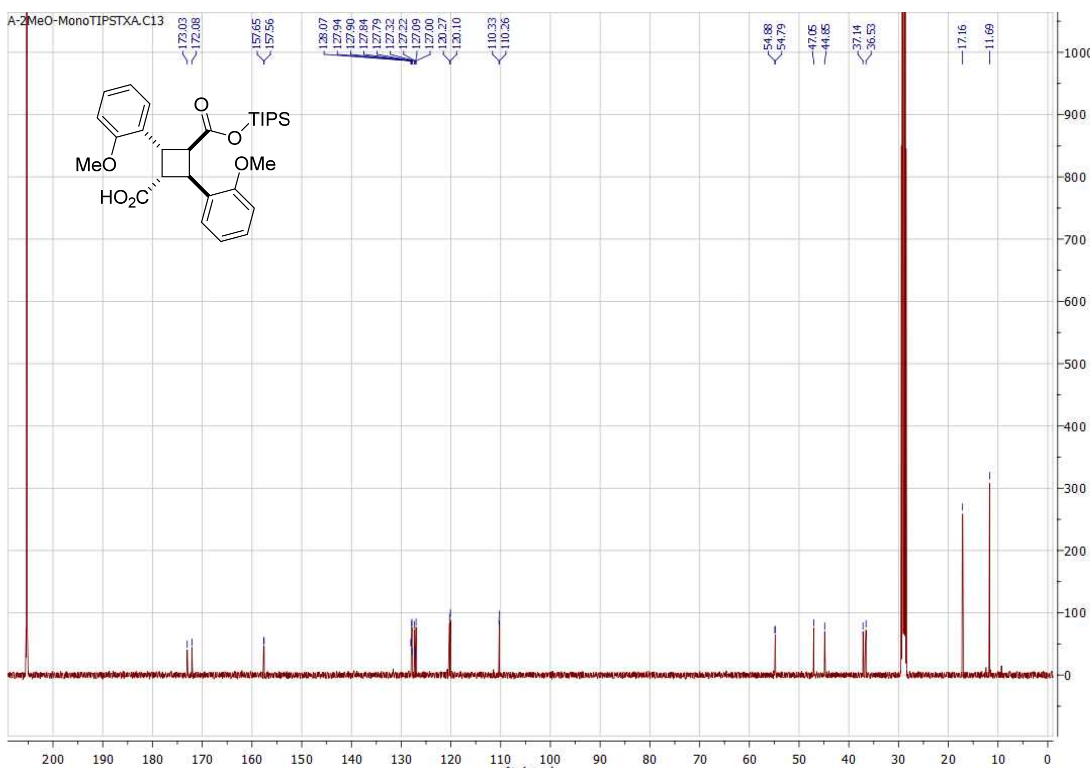

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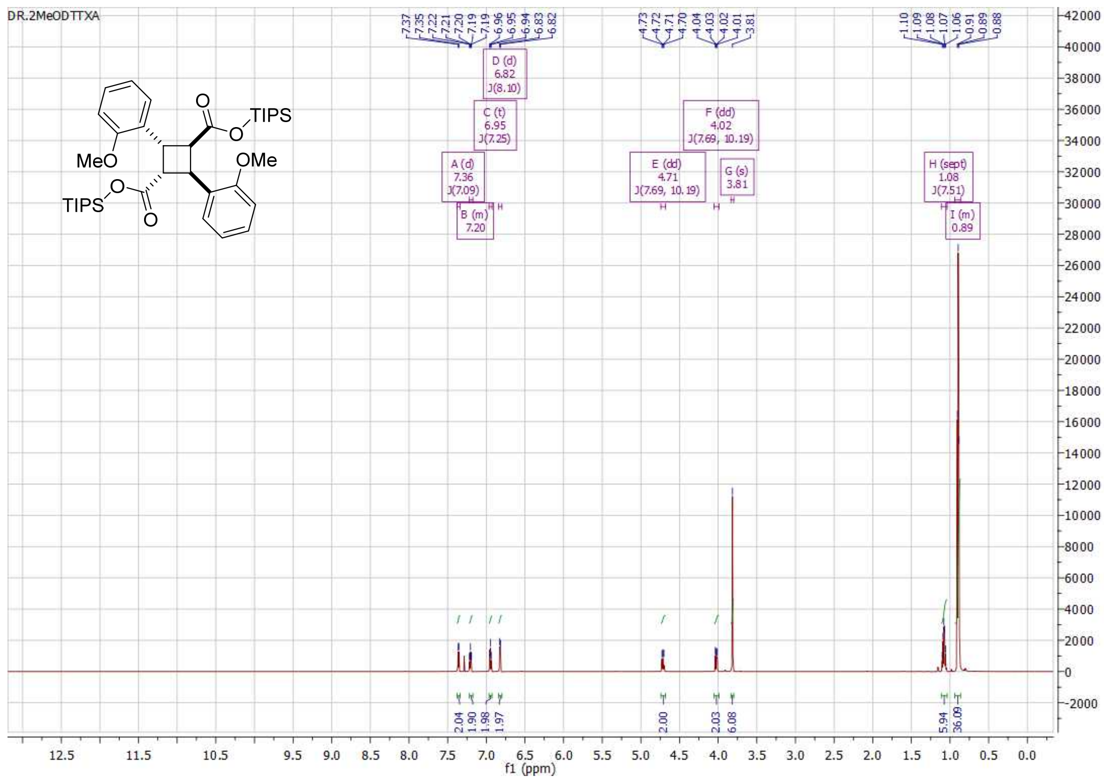

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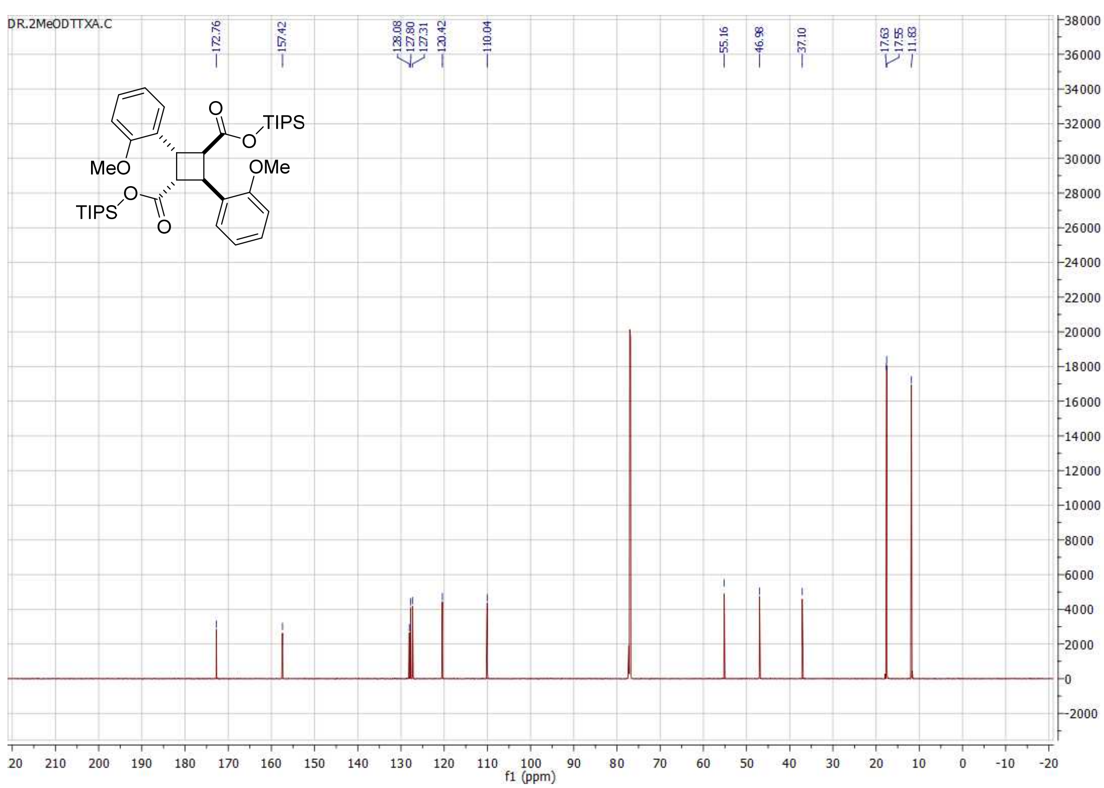
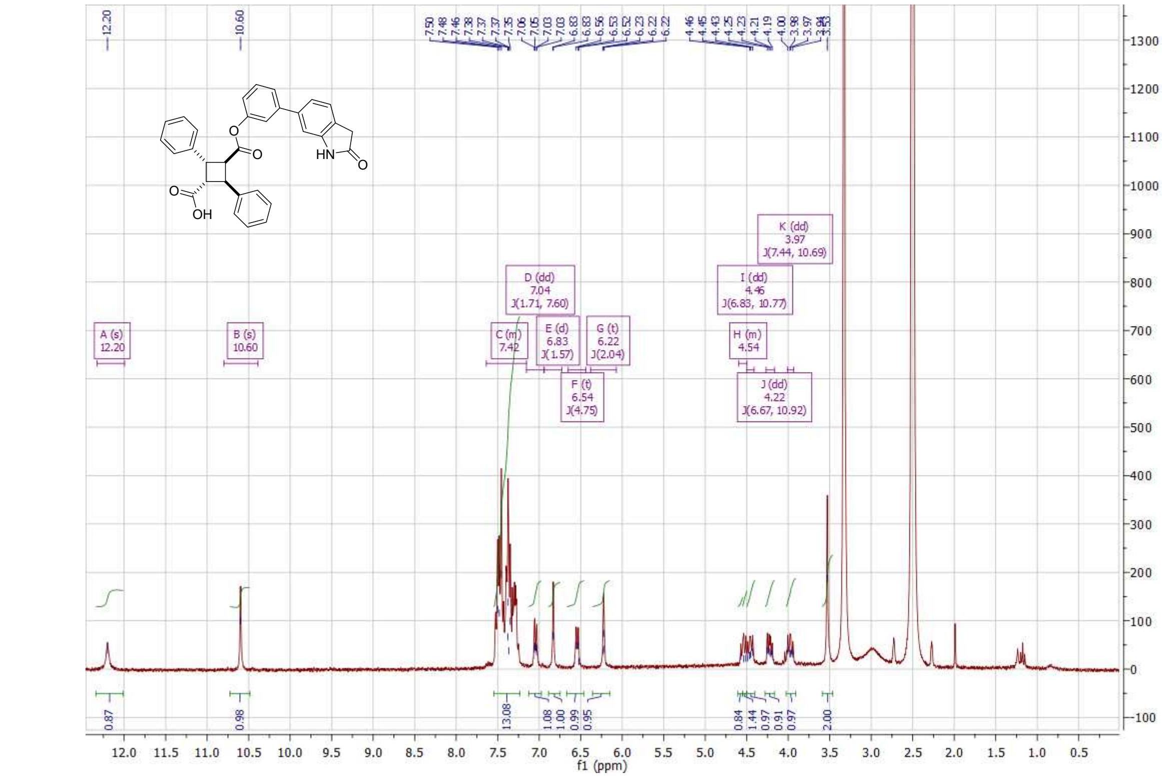
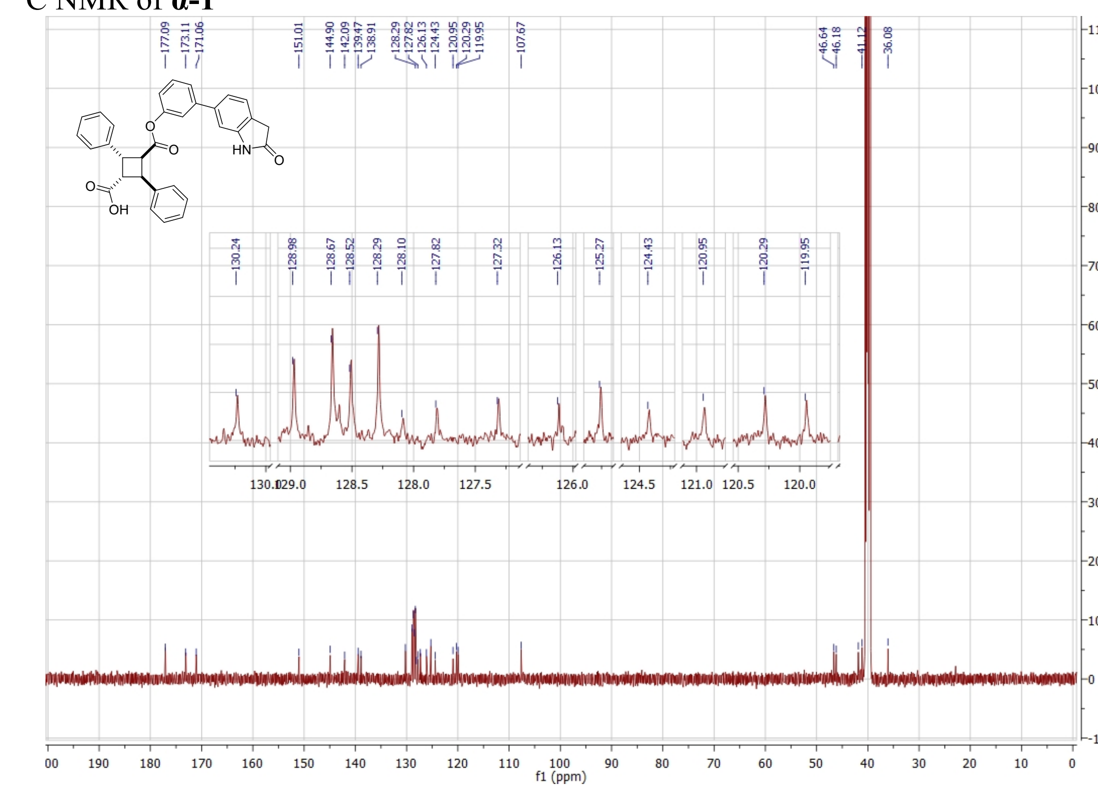


[1]H NMR of **α-1**



[13]C NMR of **α-1**



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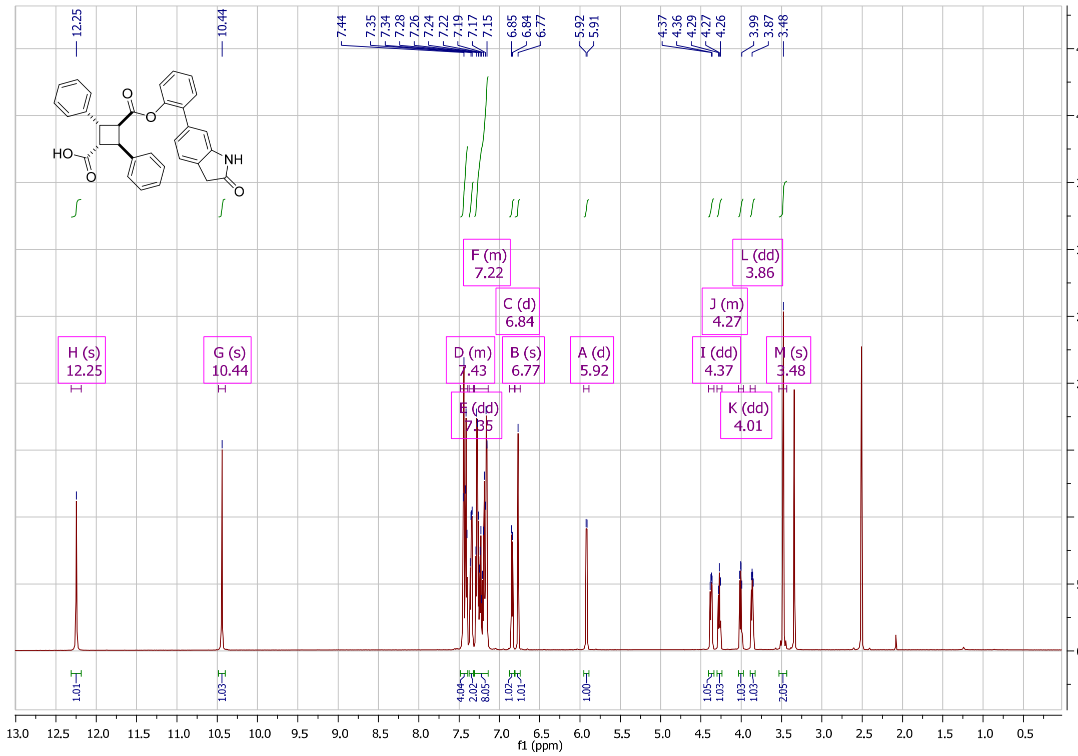

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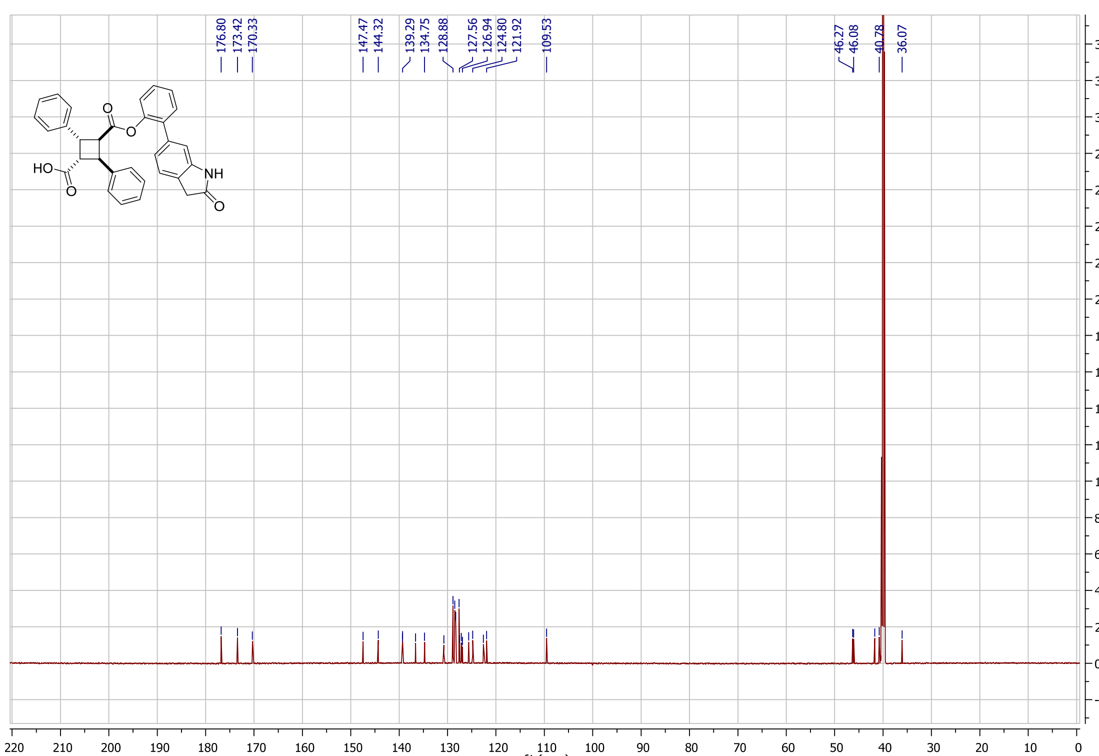
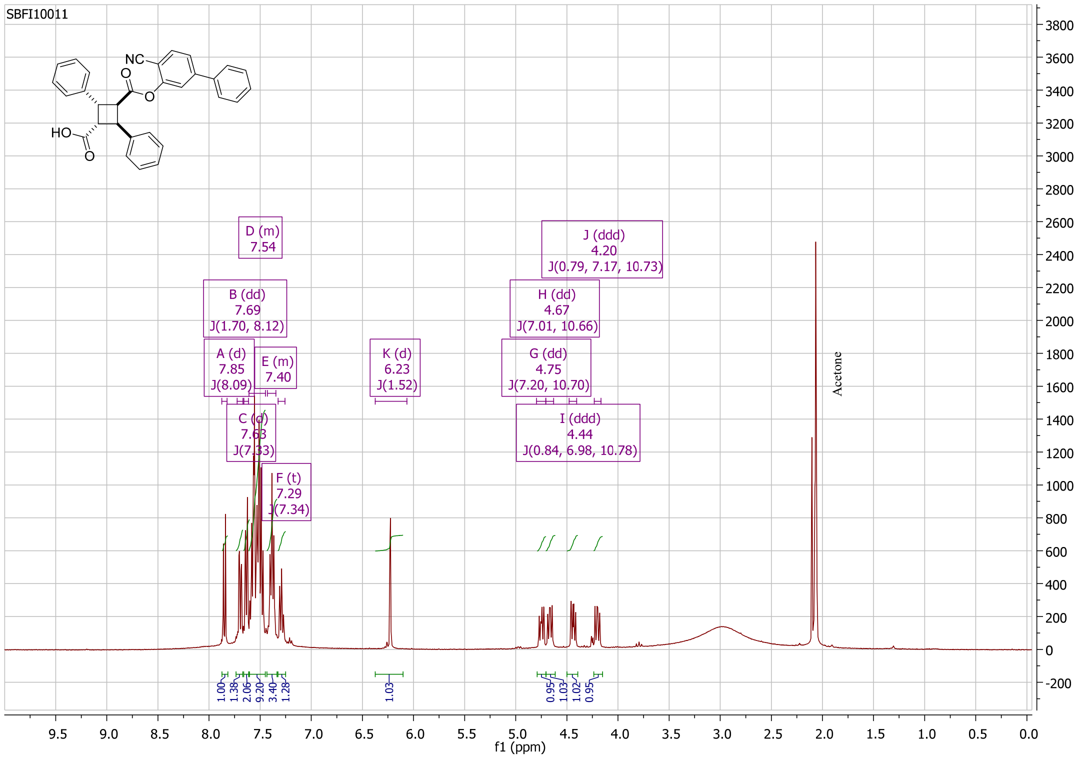


^{1}H NMR of **α-3**



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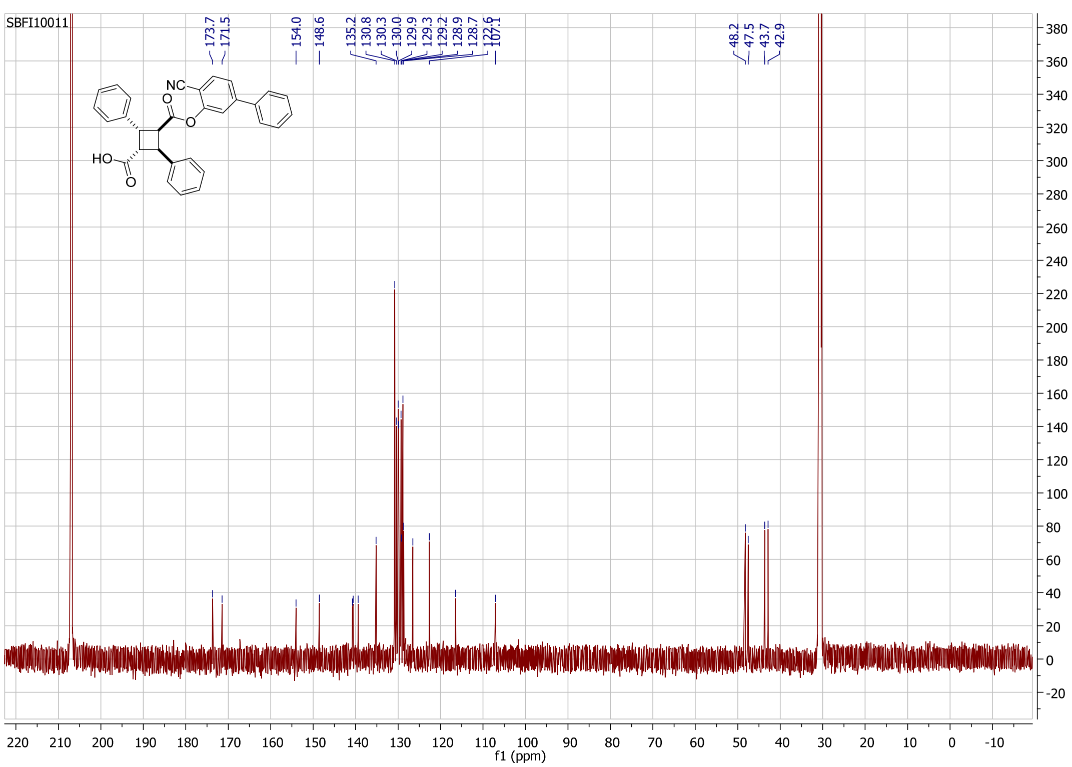

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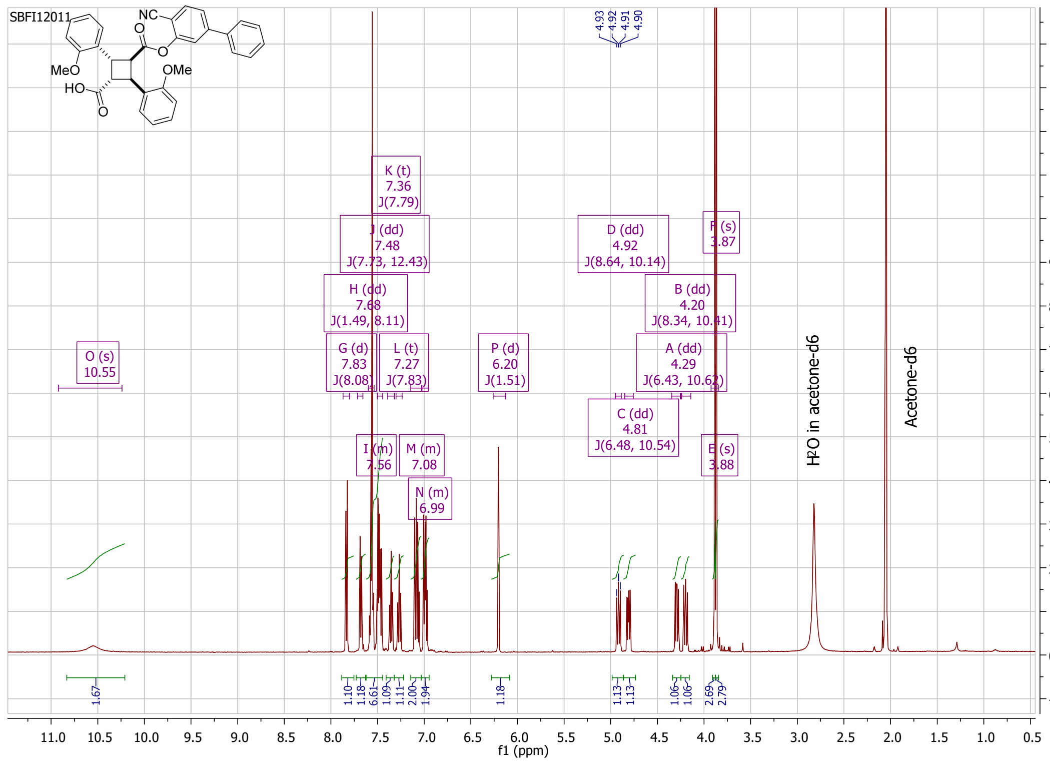

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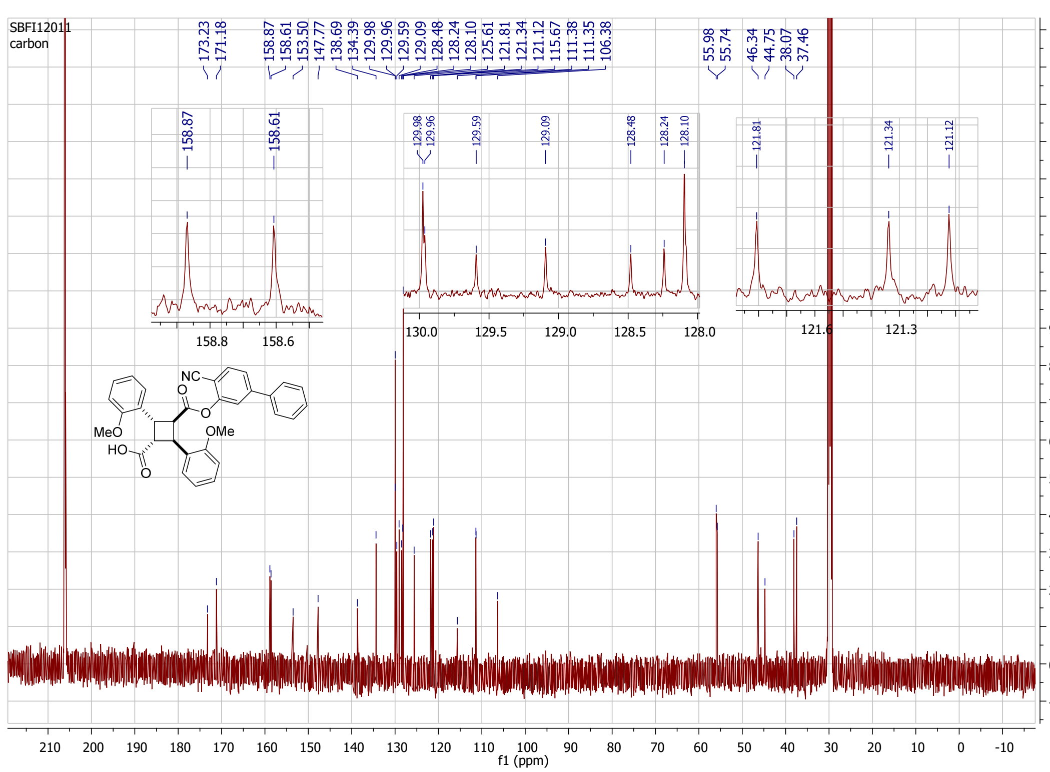
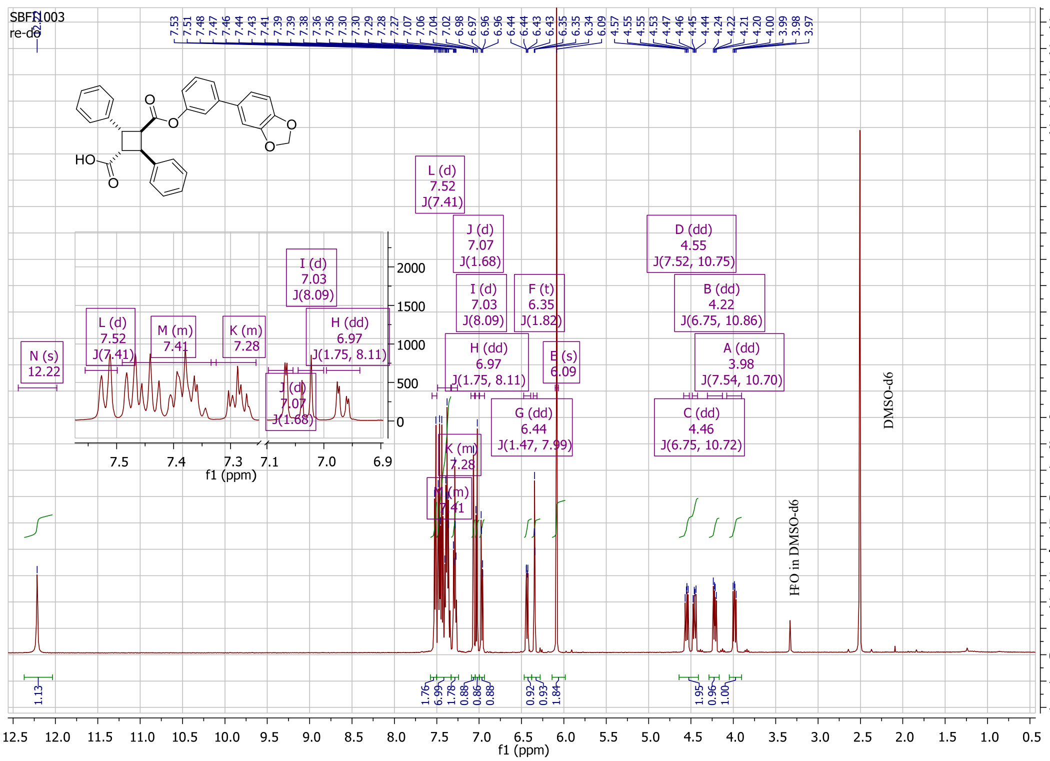


^{1}H NMR of **α-5**



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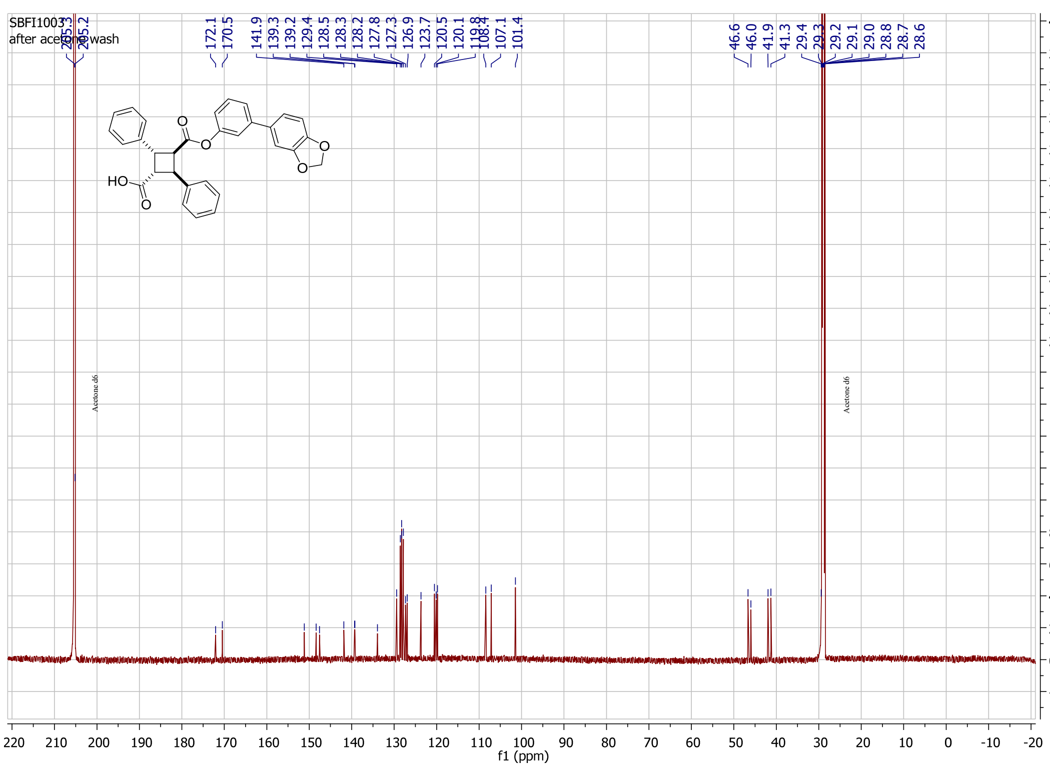

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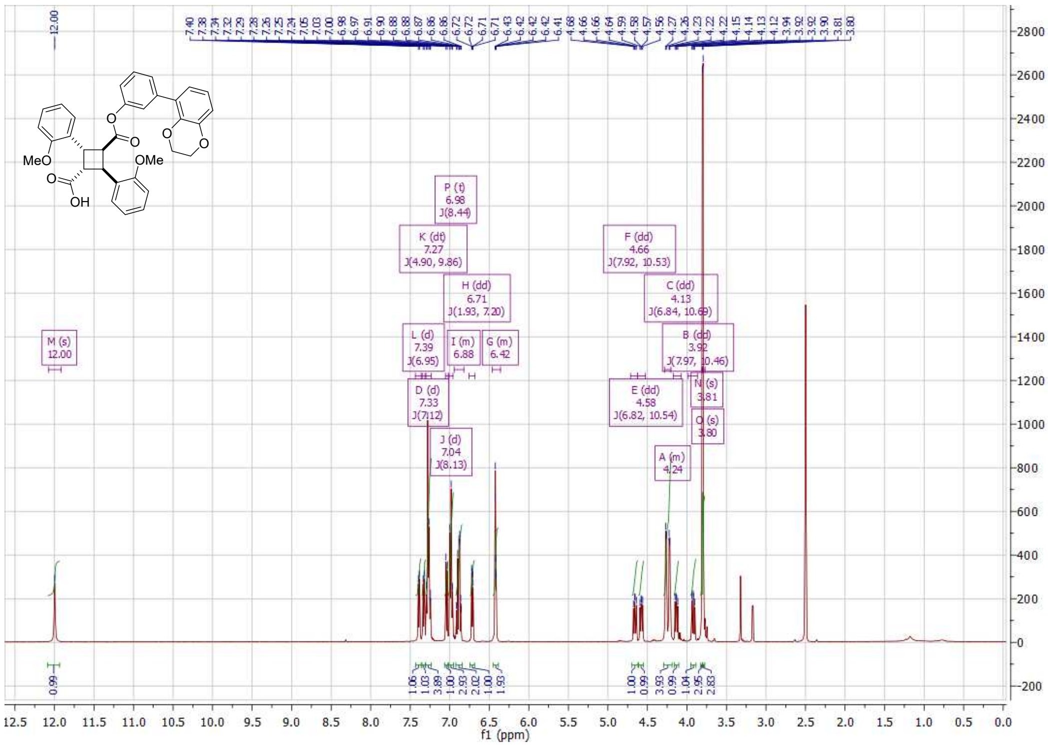

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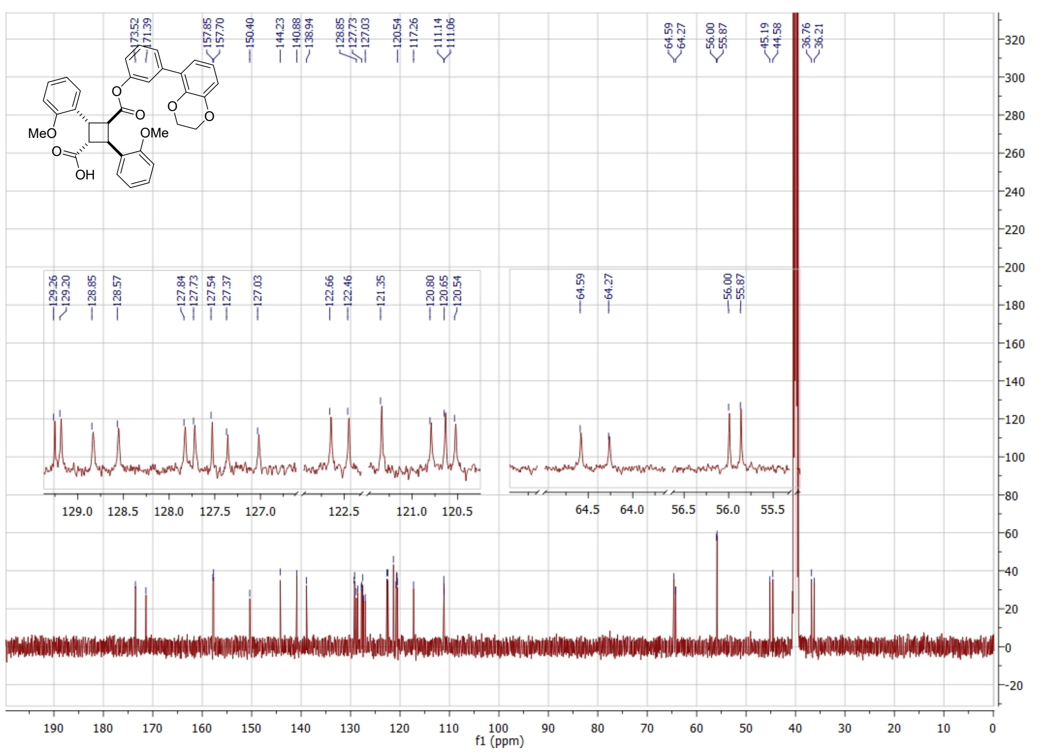
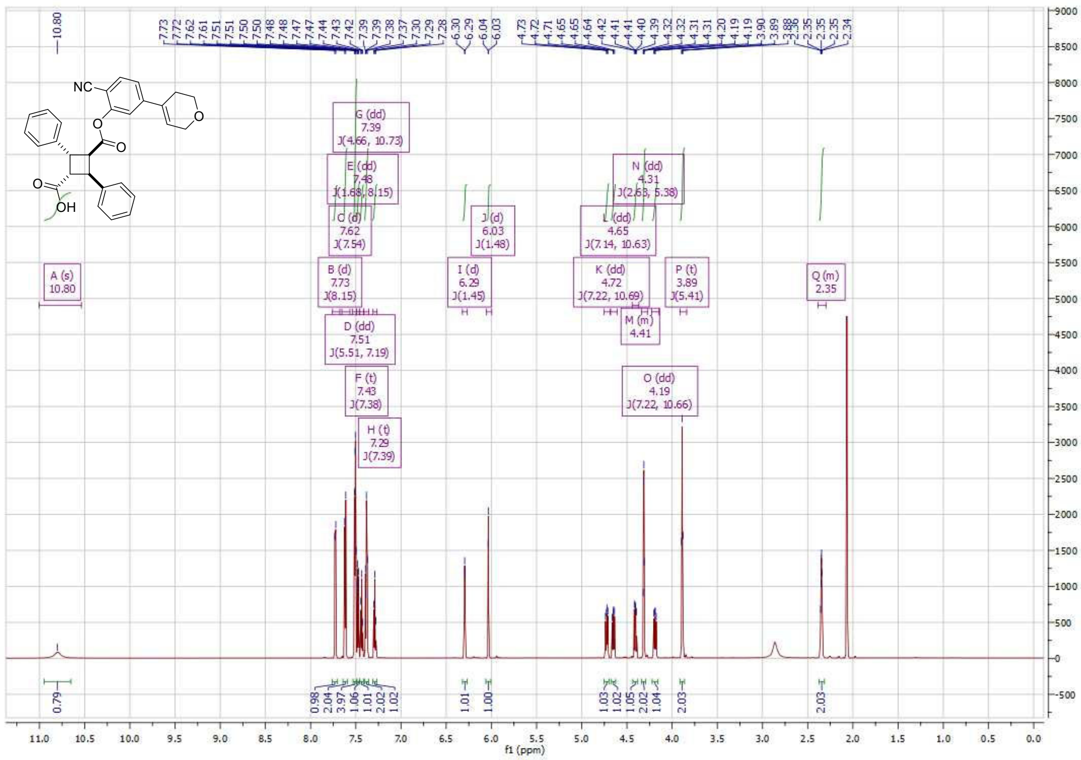
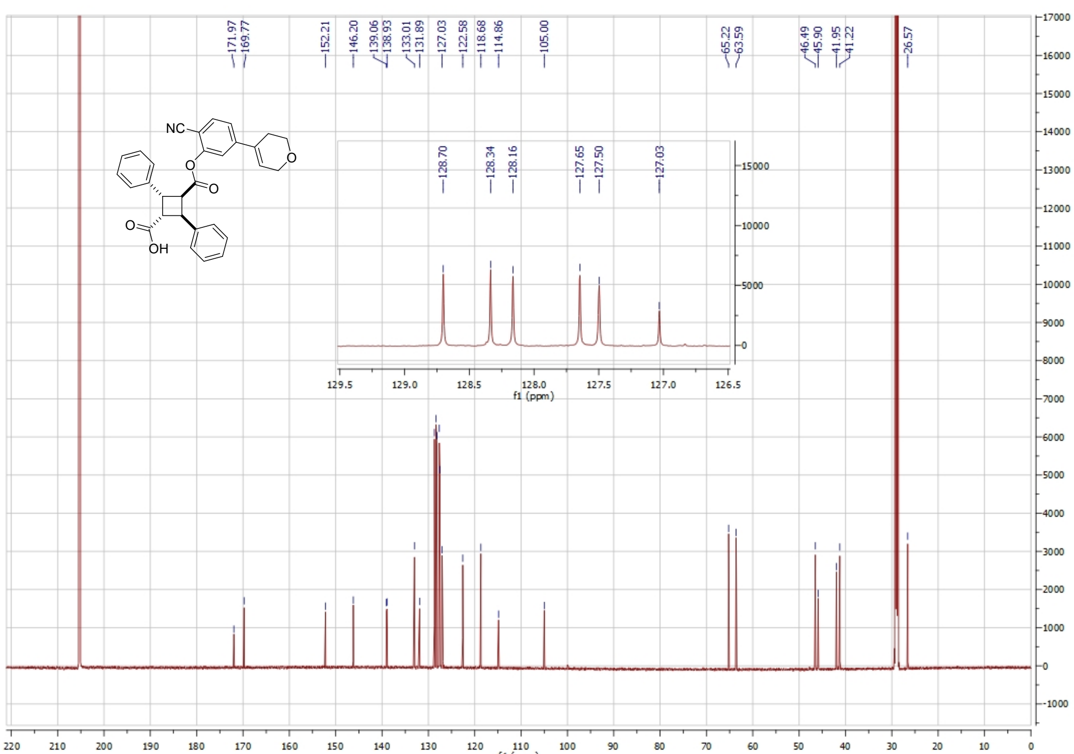


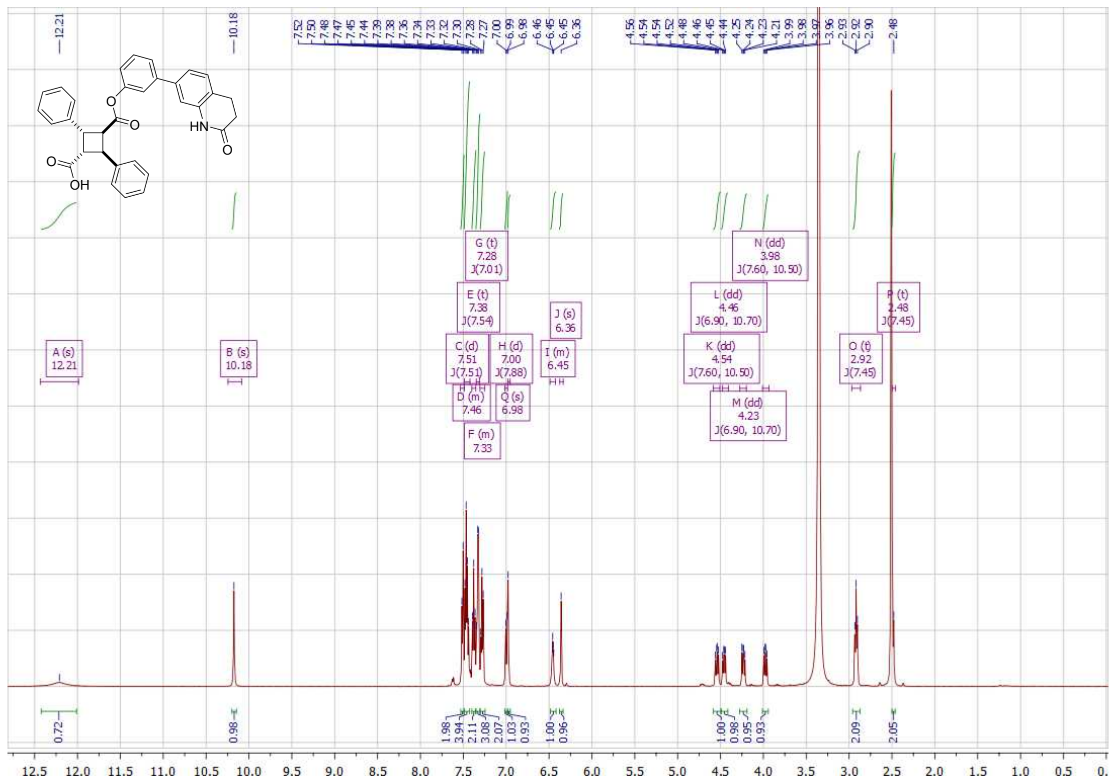
^{1}H NMR of **α-7**



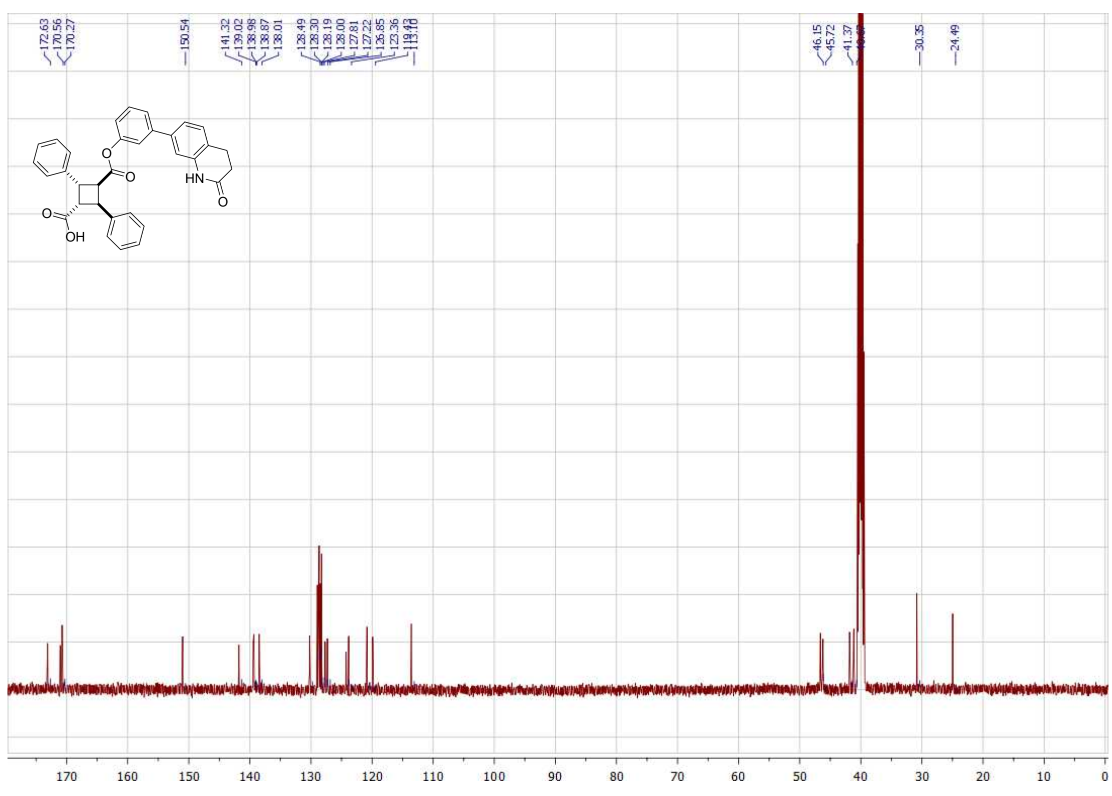
^{13}C NMR of **α-7**



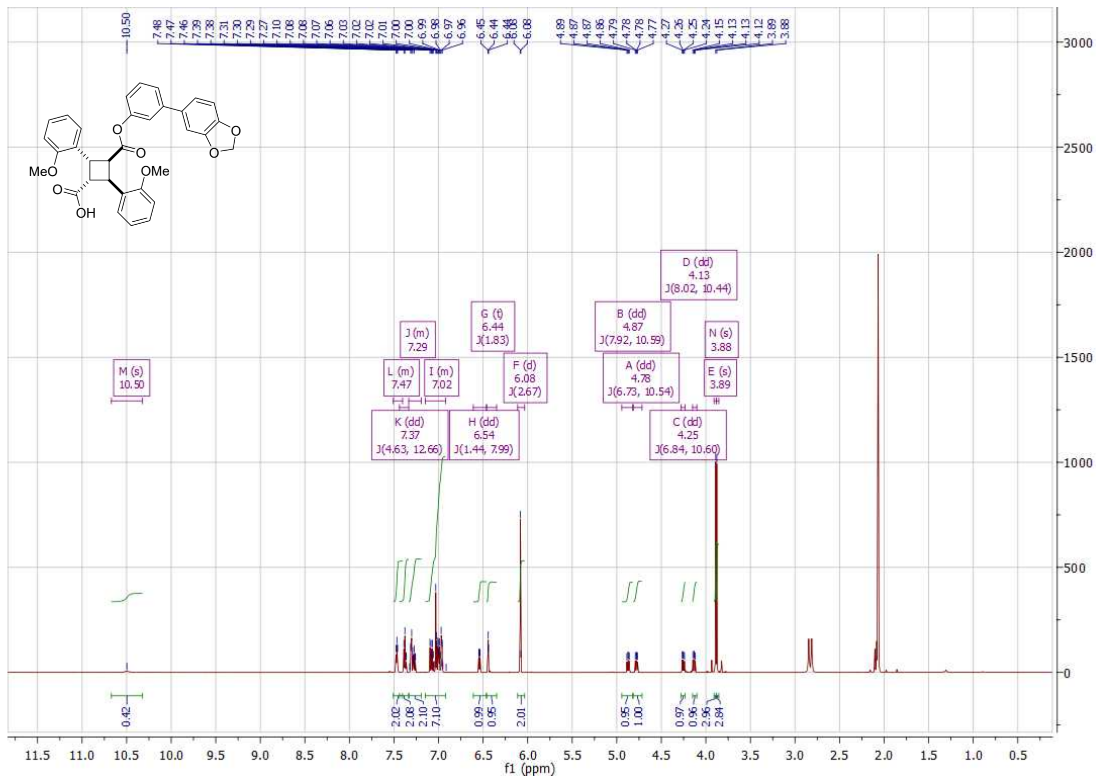
^{1}H NMR of **α-8**



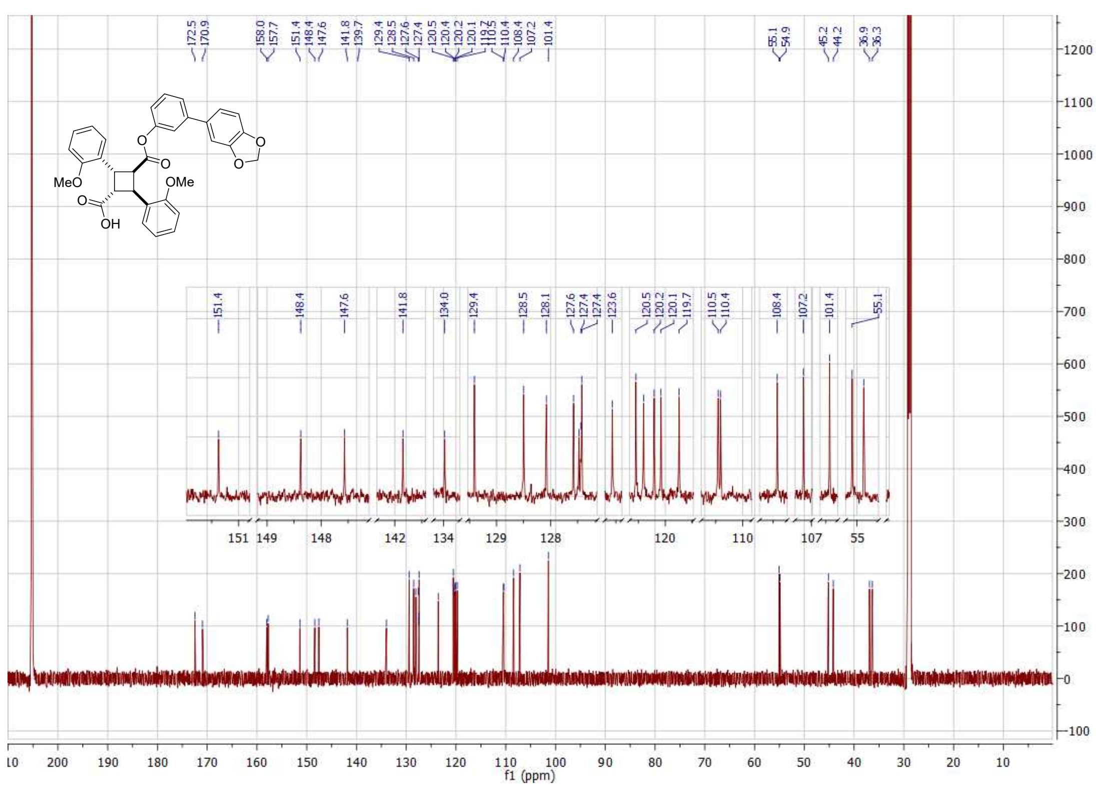
^{13}C NMR of **α-8**



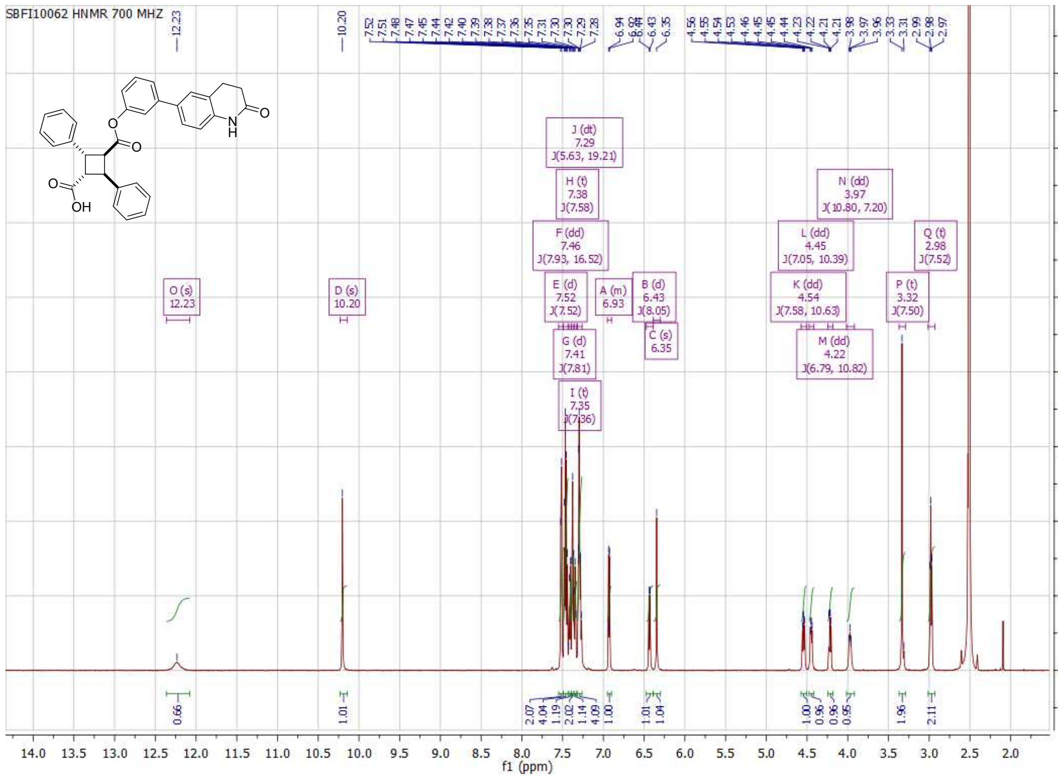
^{1}H NMR of **α-9**



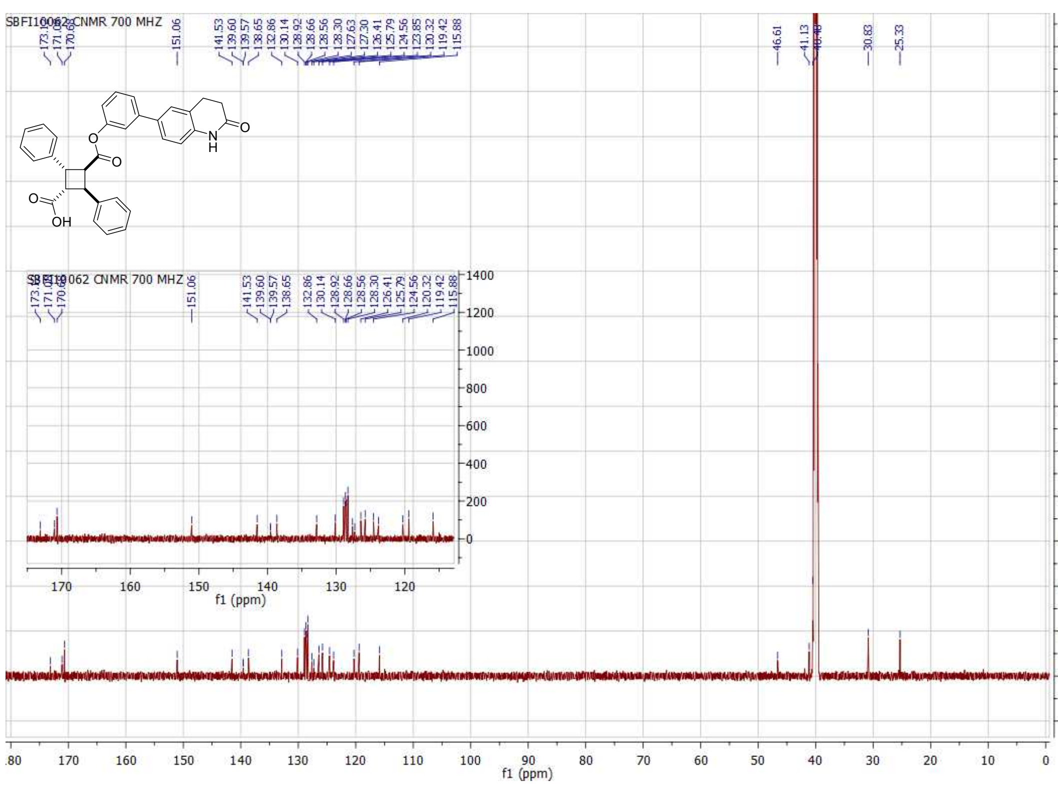
^{13}C NMR of **α-9**



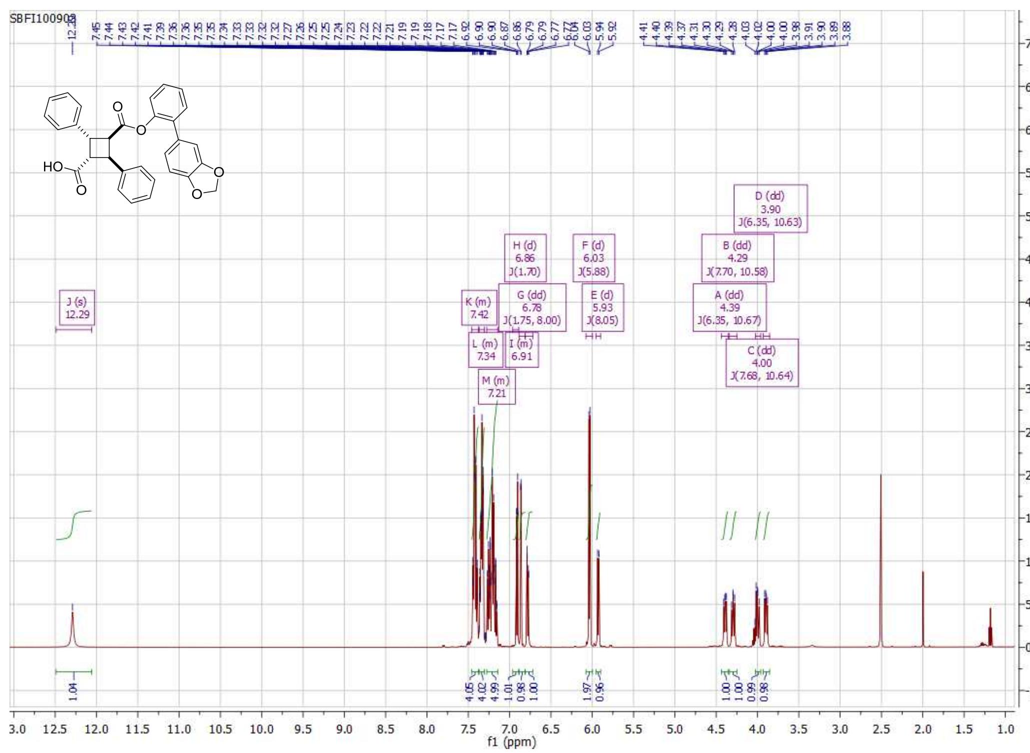
[1]H NMR of **α-10**



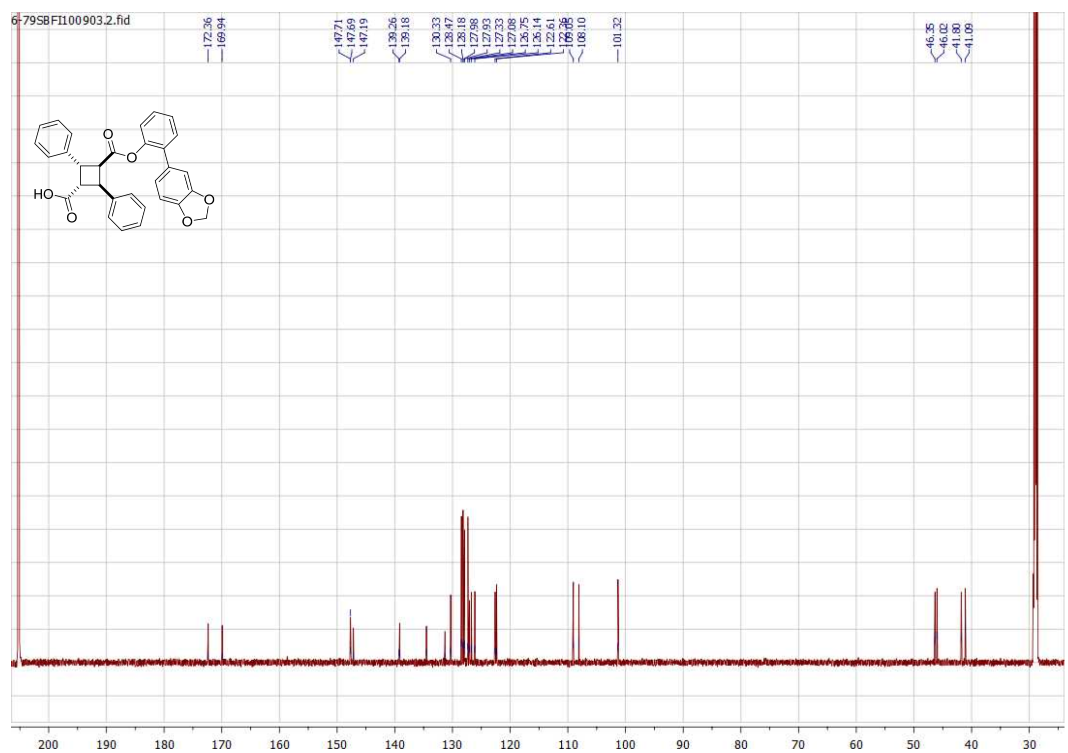
[13]C NMR of **α-10**



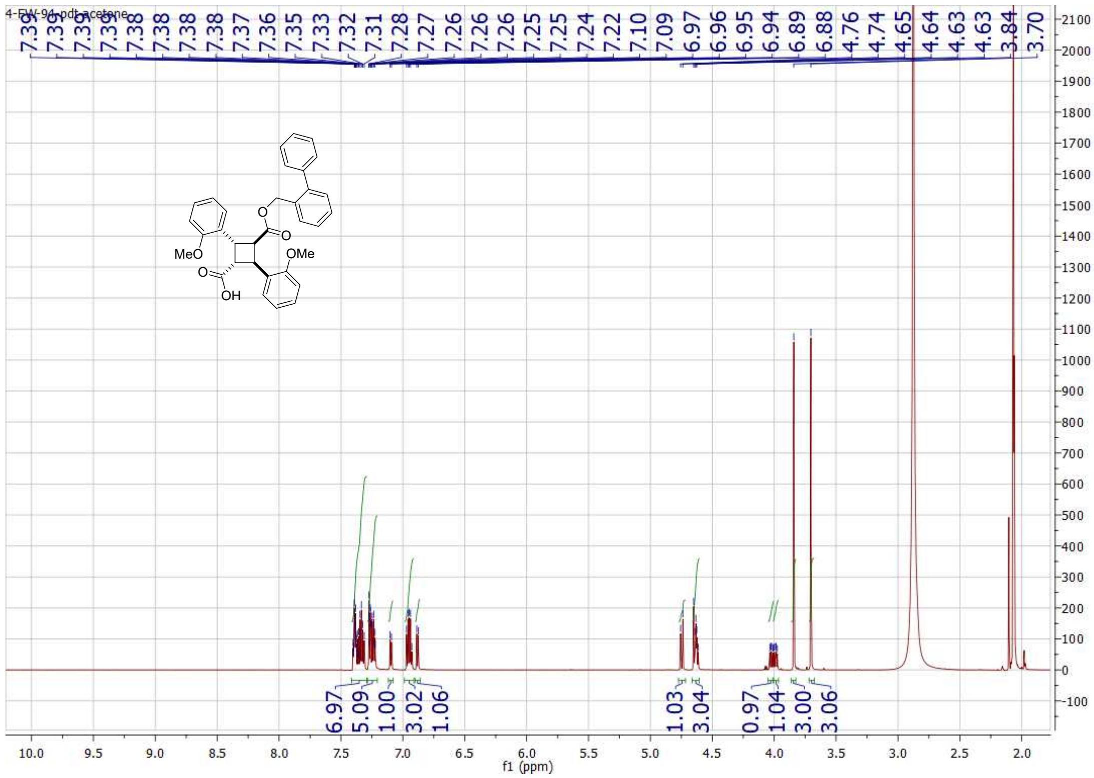
[1]H NMR of **α-11**



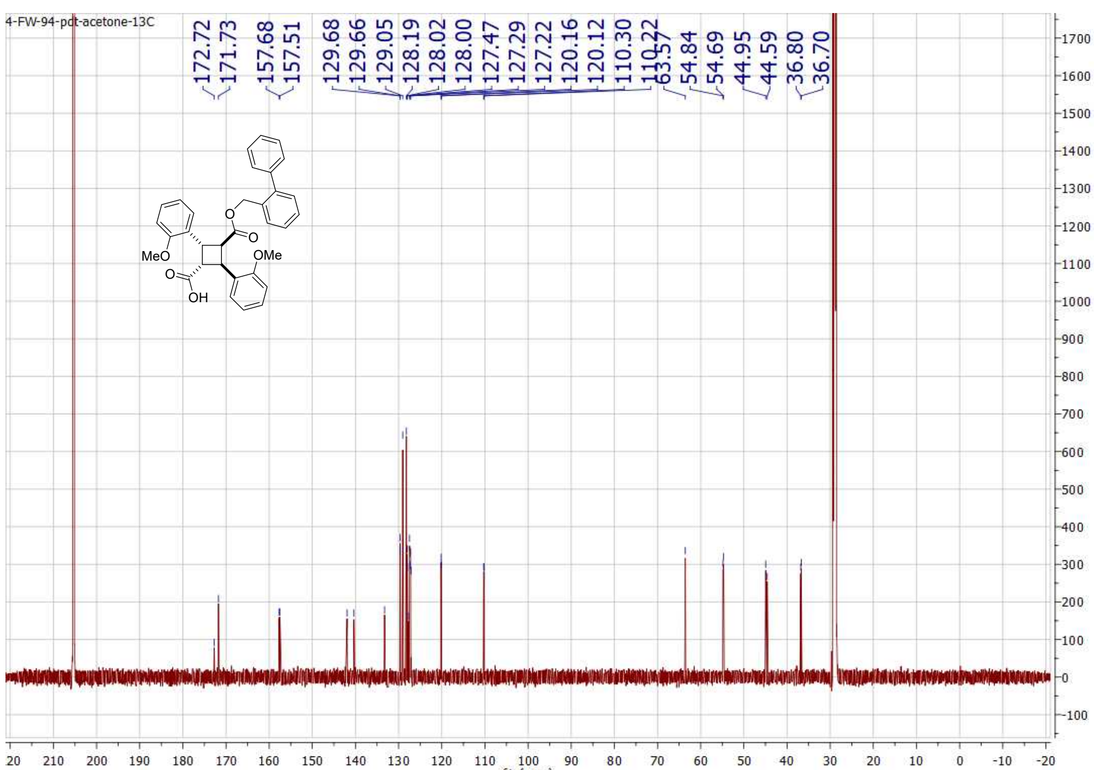
[13]C NMR of **α-11**



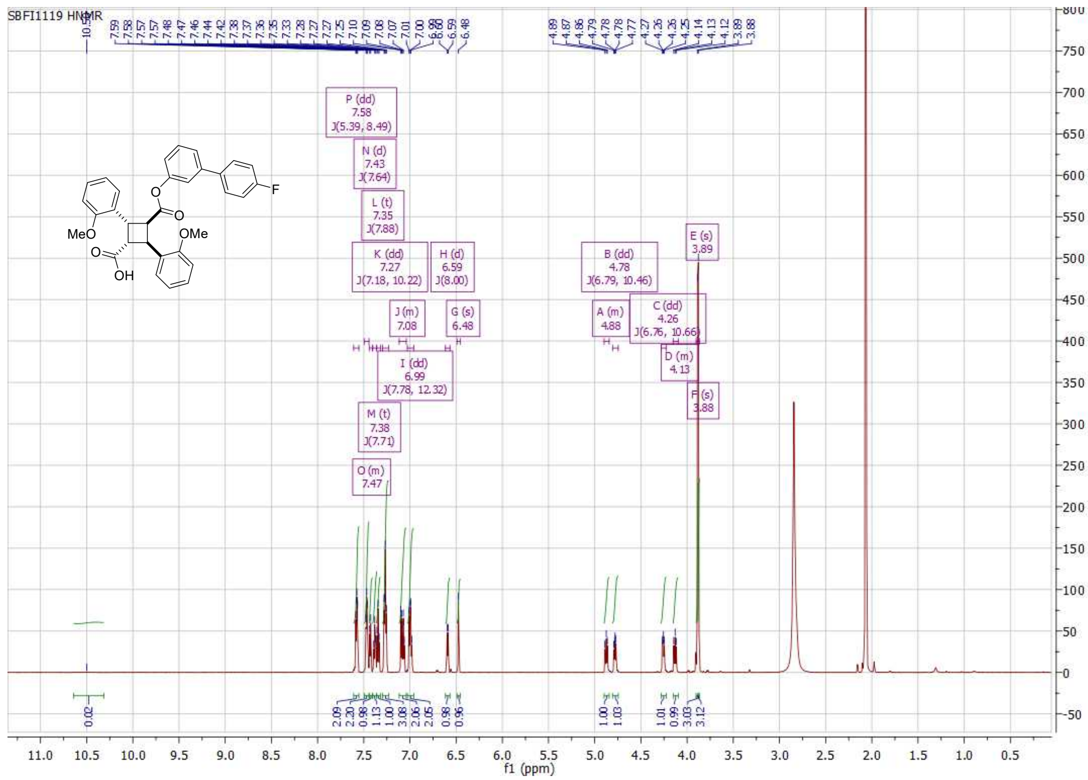
^{1}H NMR of **α-12**



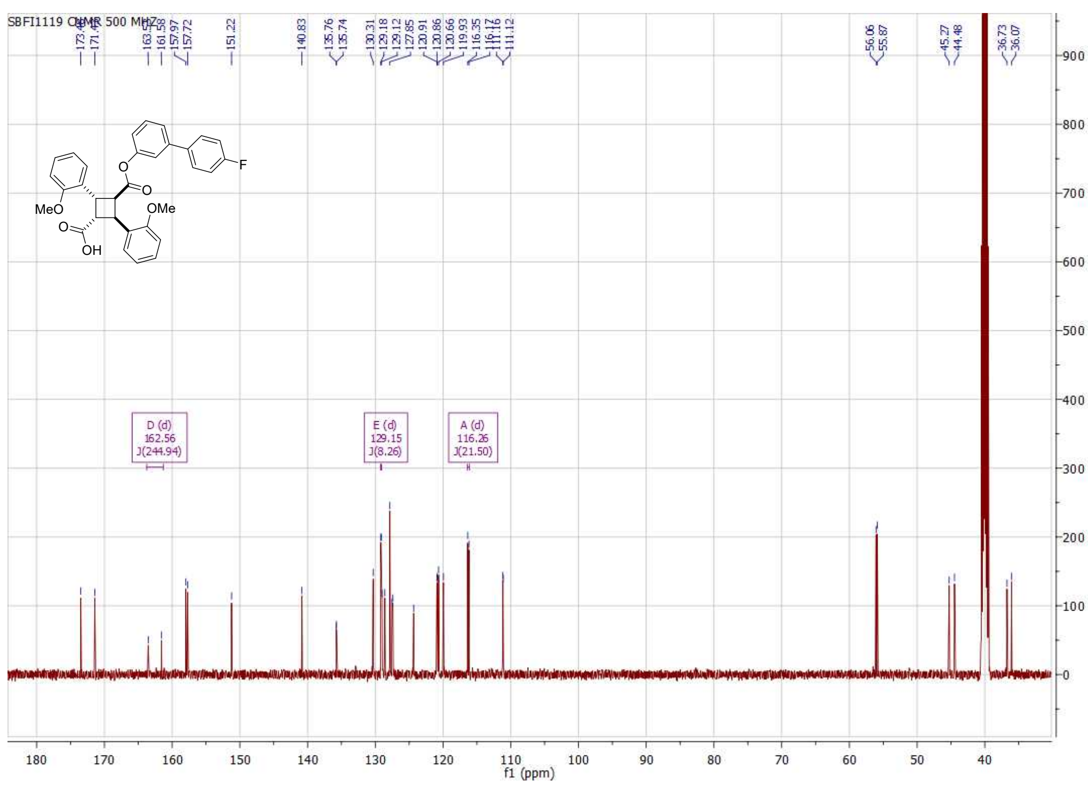
^{13}C NMR of **α-12**



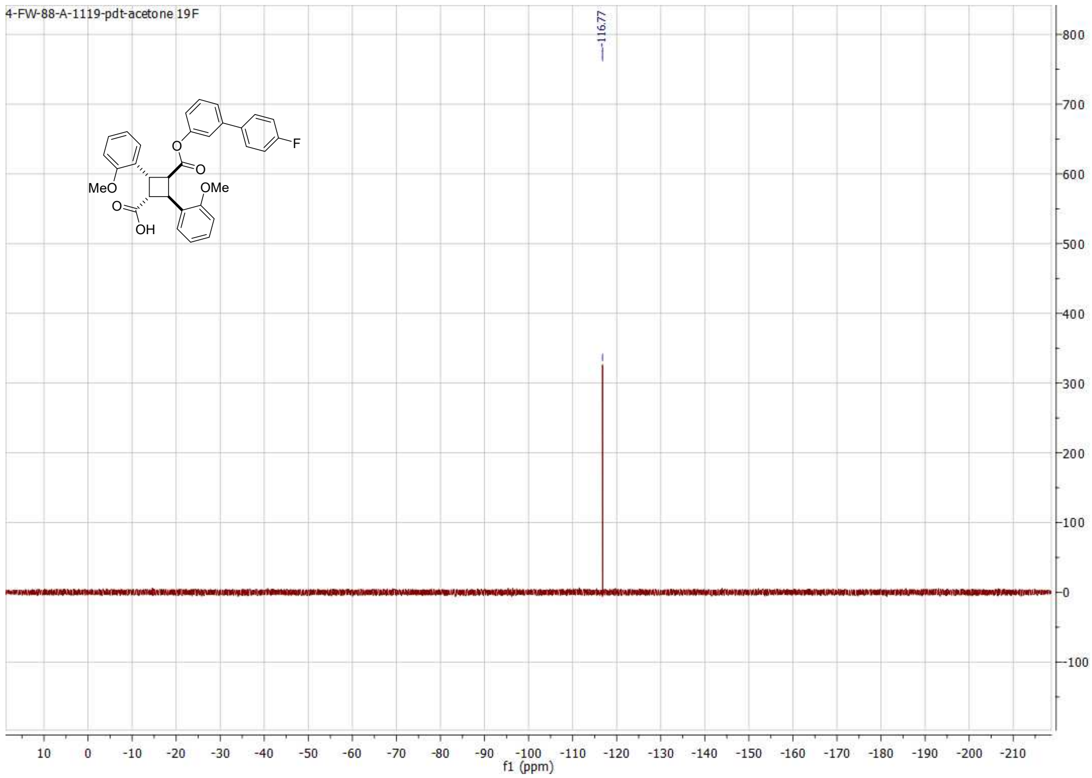
[1]H NMR of **α-13**



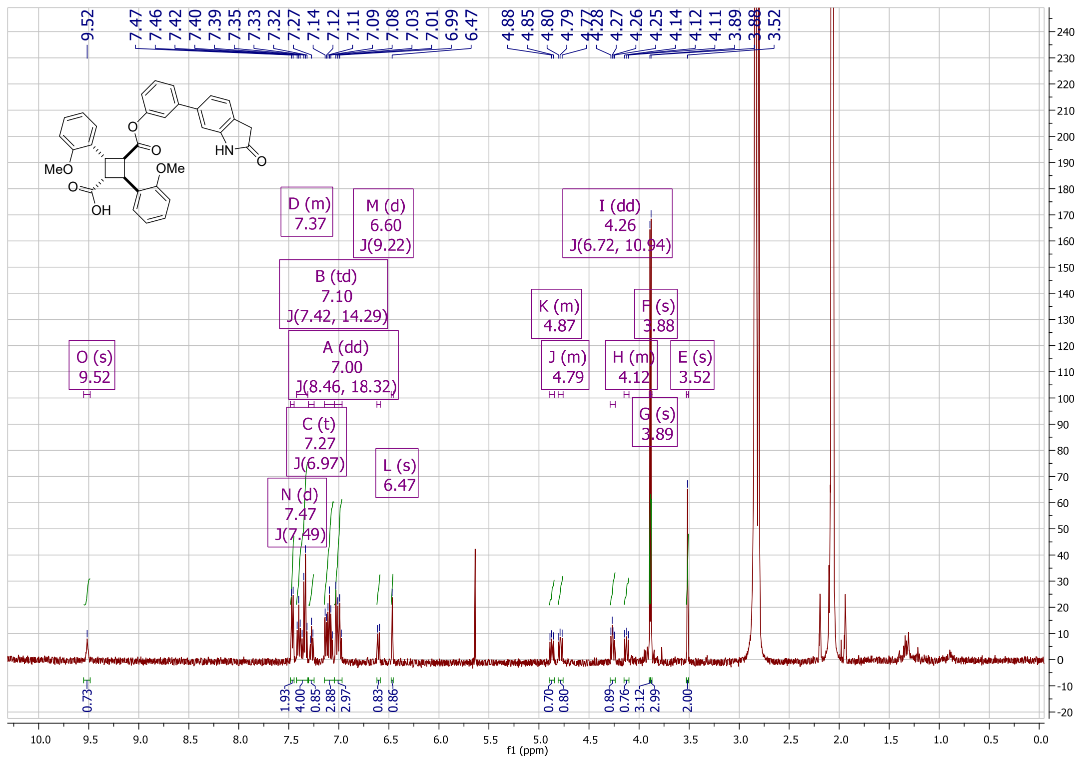
[13]C NMR of **α-13**



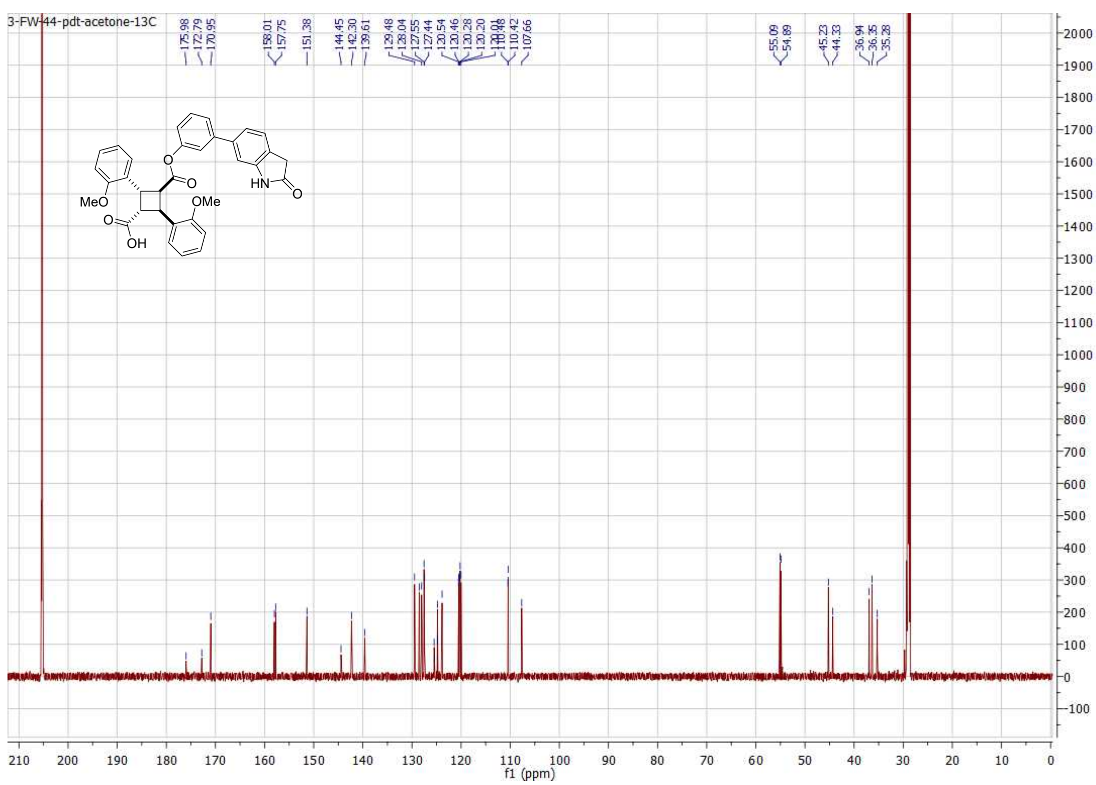
^{19}F NMR of **α-13**



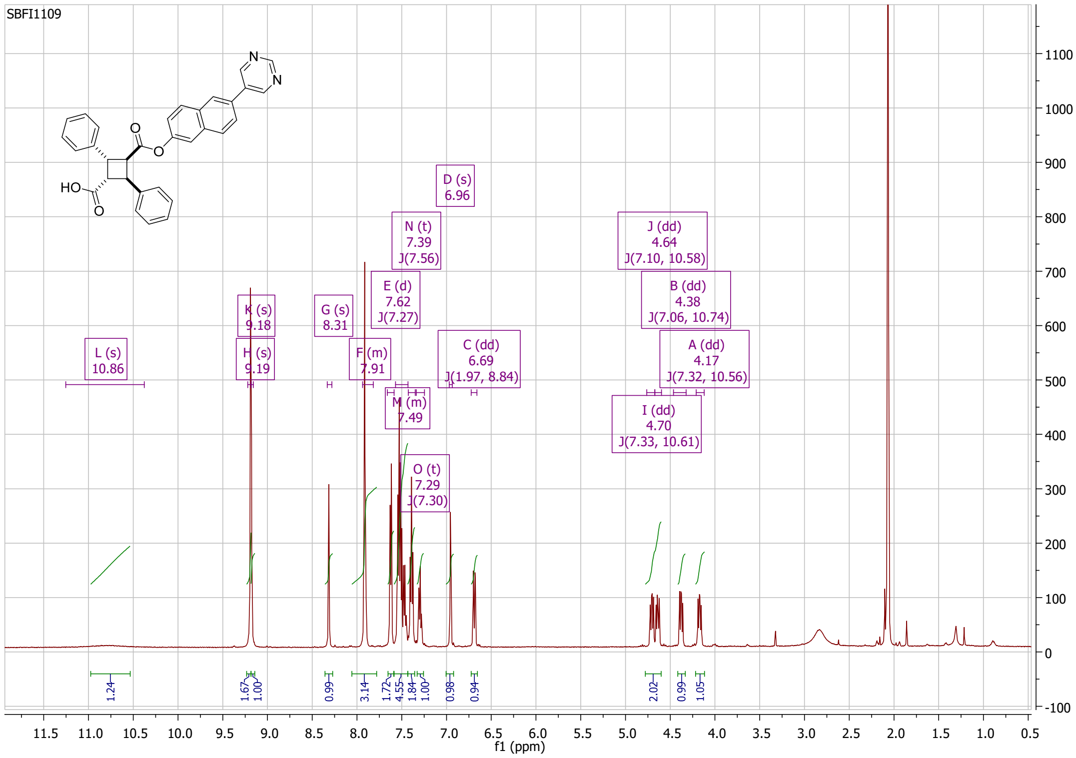
^{1}H NMR of **α-14**



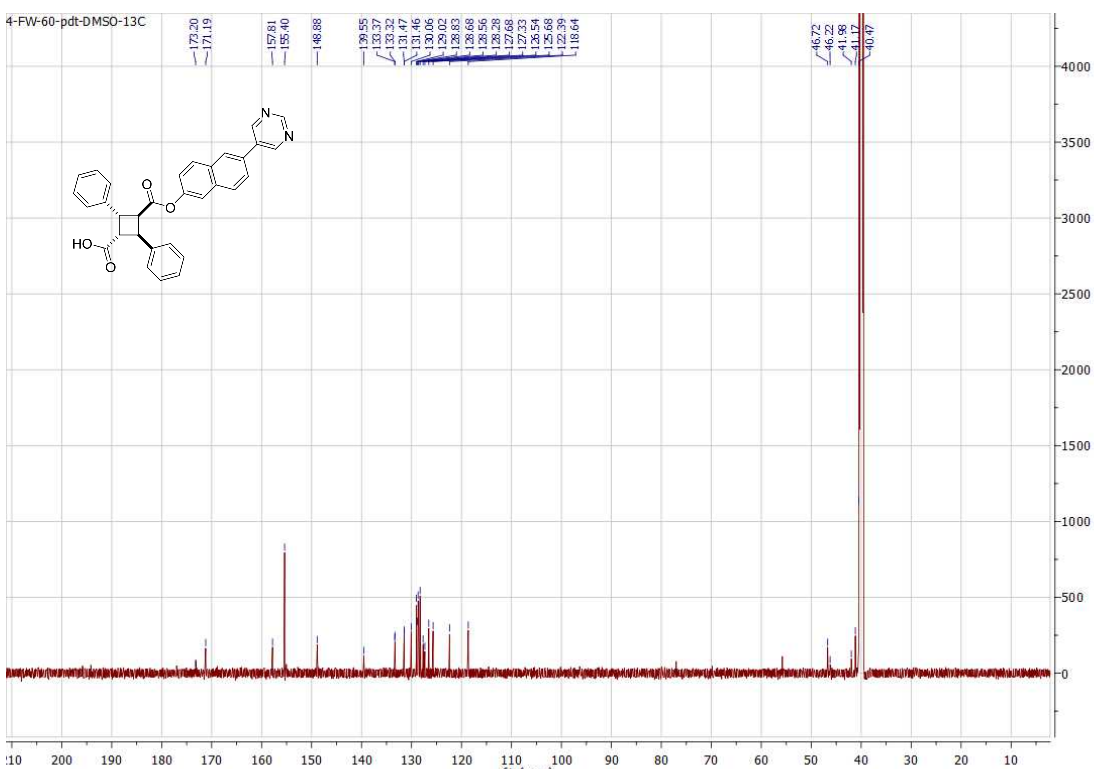
^{13}C NMR of **α-14**



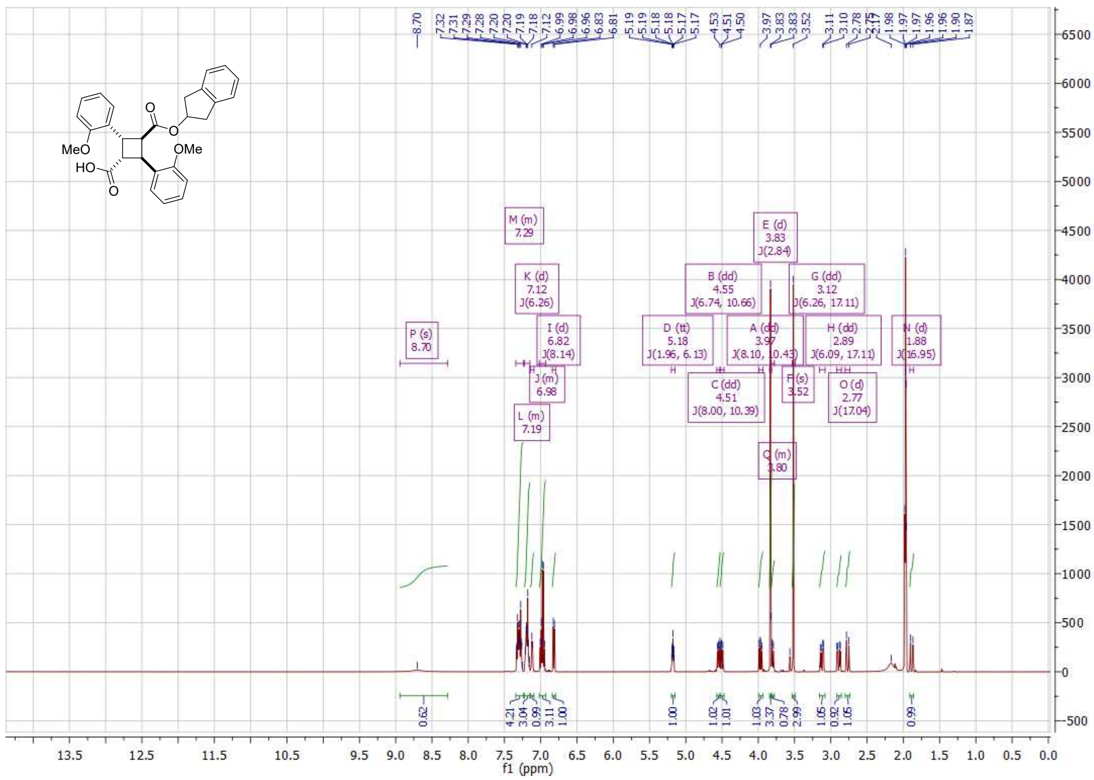
[1]H NMR of **α-15**



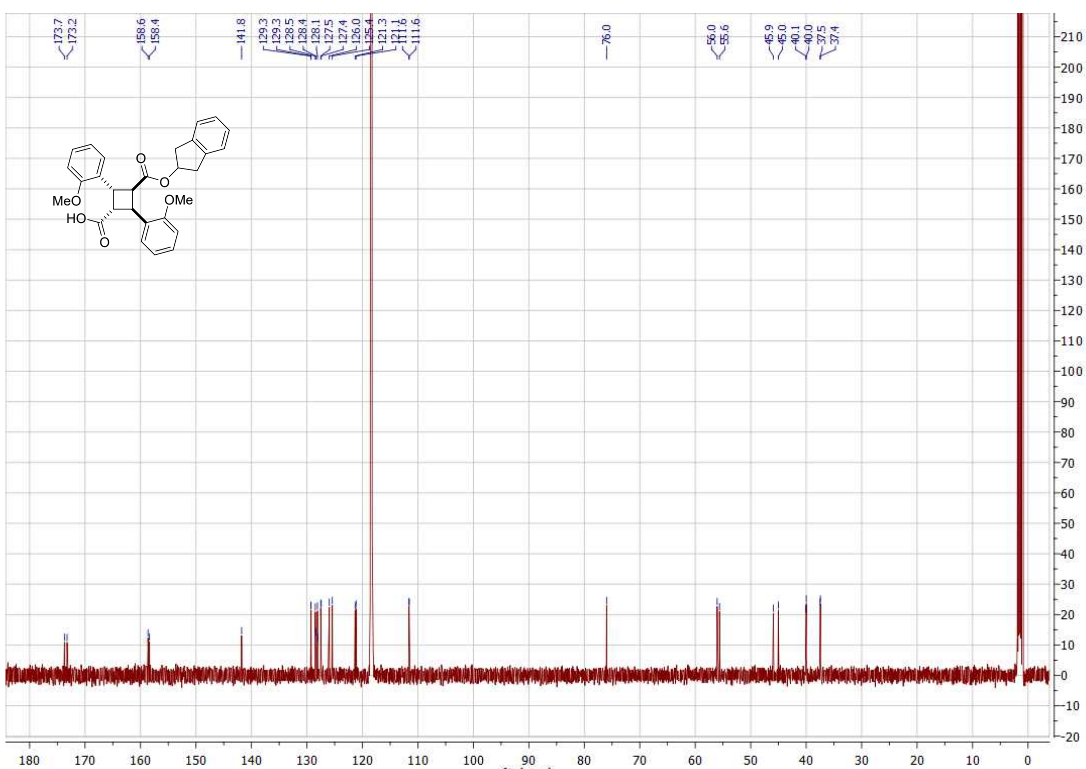
[13]C NMR of **α-15**



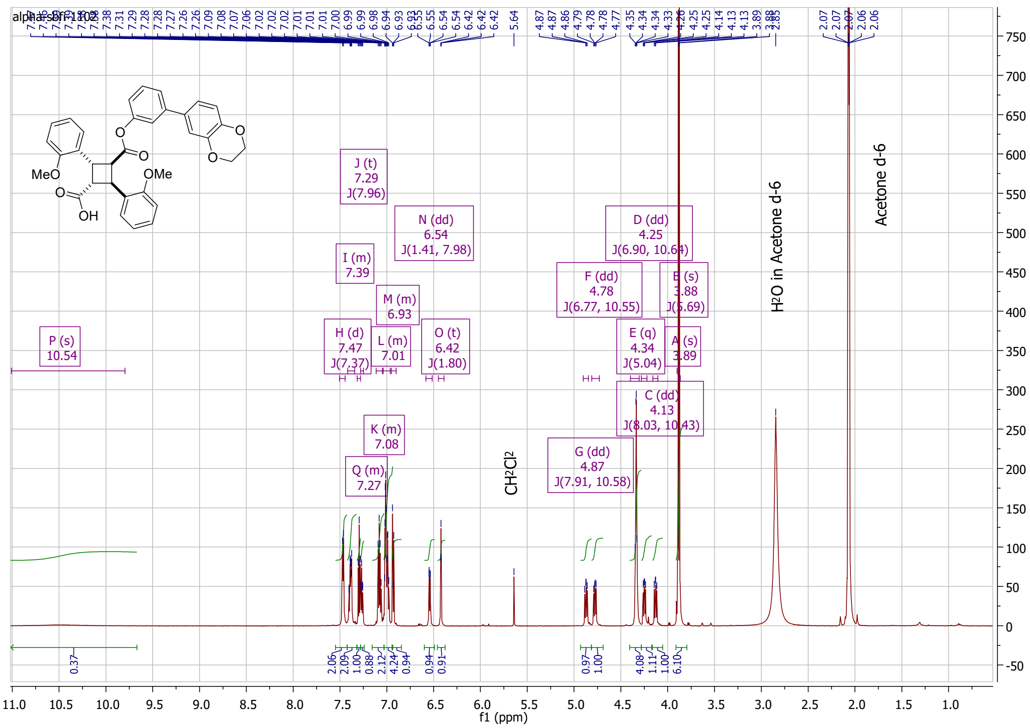
[1]H NMR of **α-16**



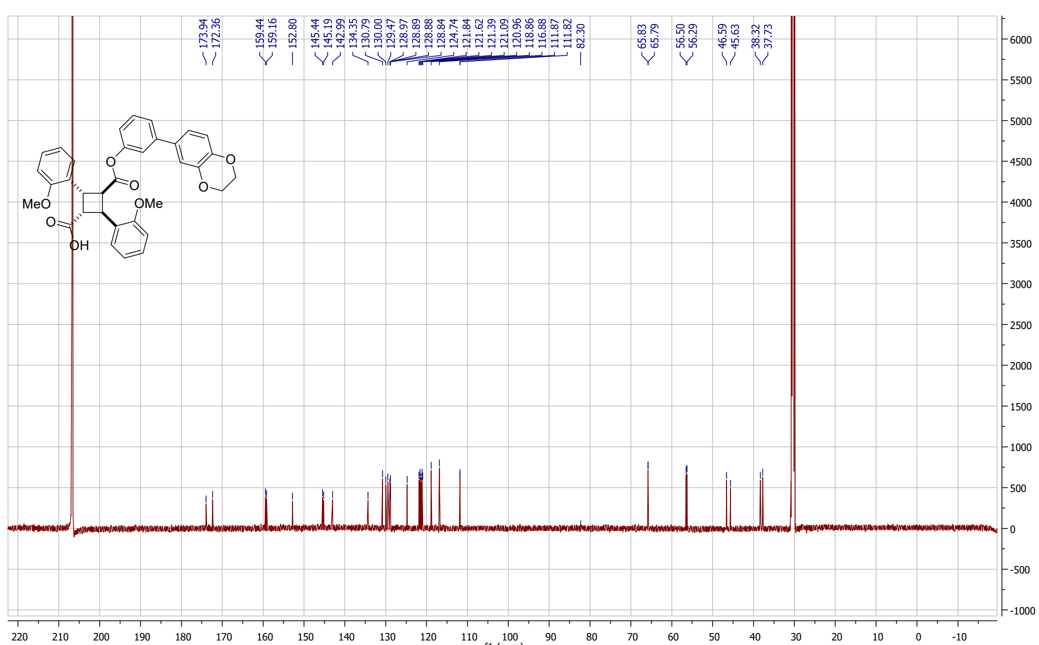
[13]C NMR of **α-16**



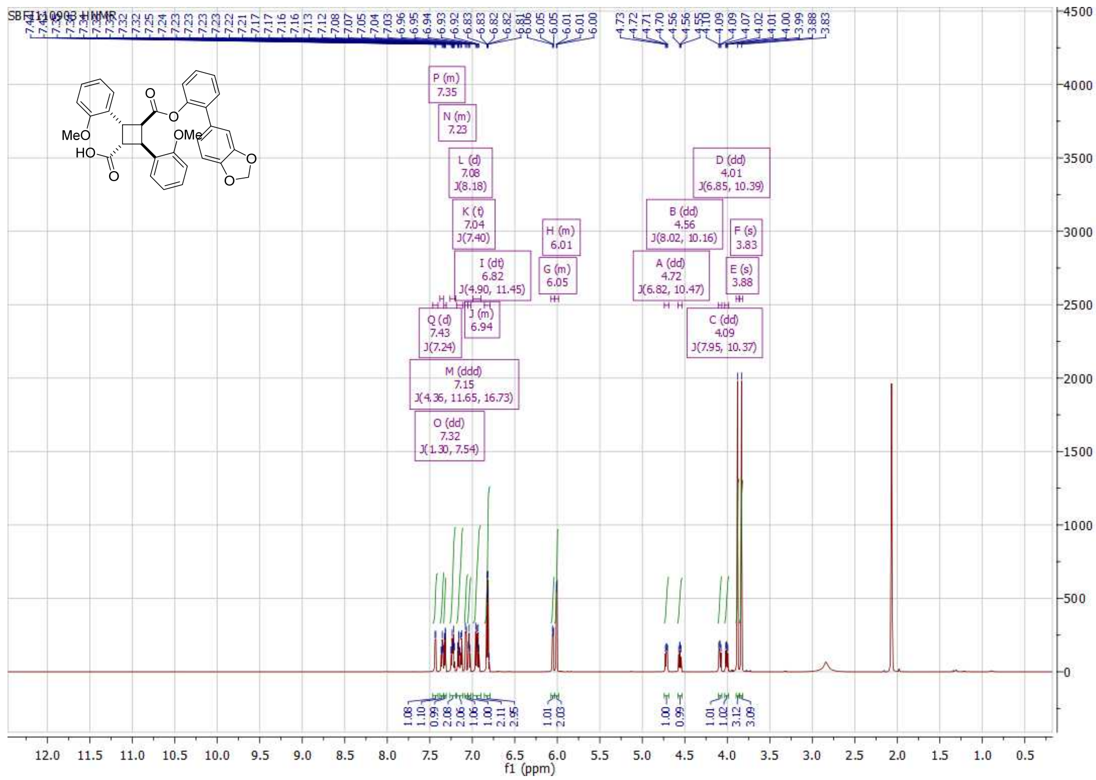
^{1}H NMR of **α-17**



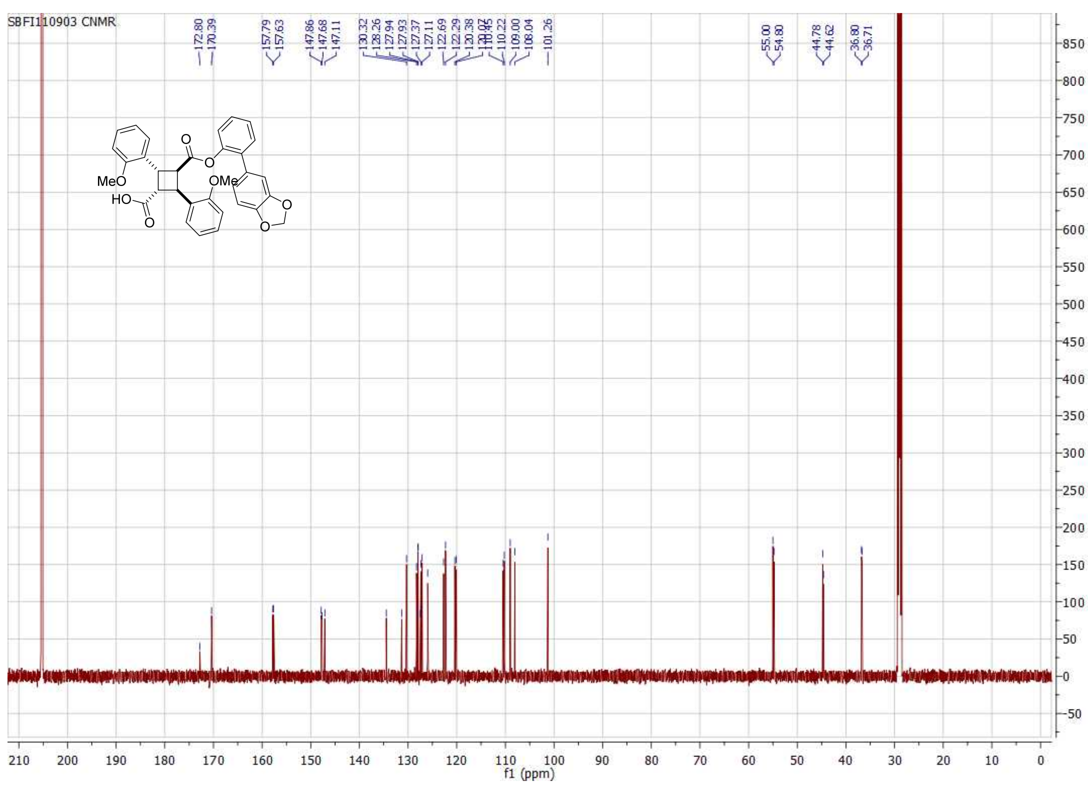
^{13}C NMR of **α-17**



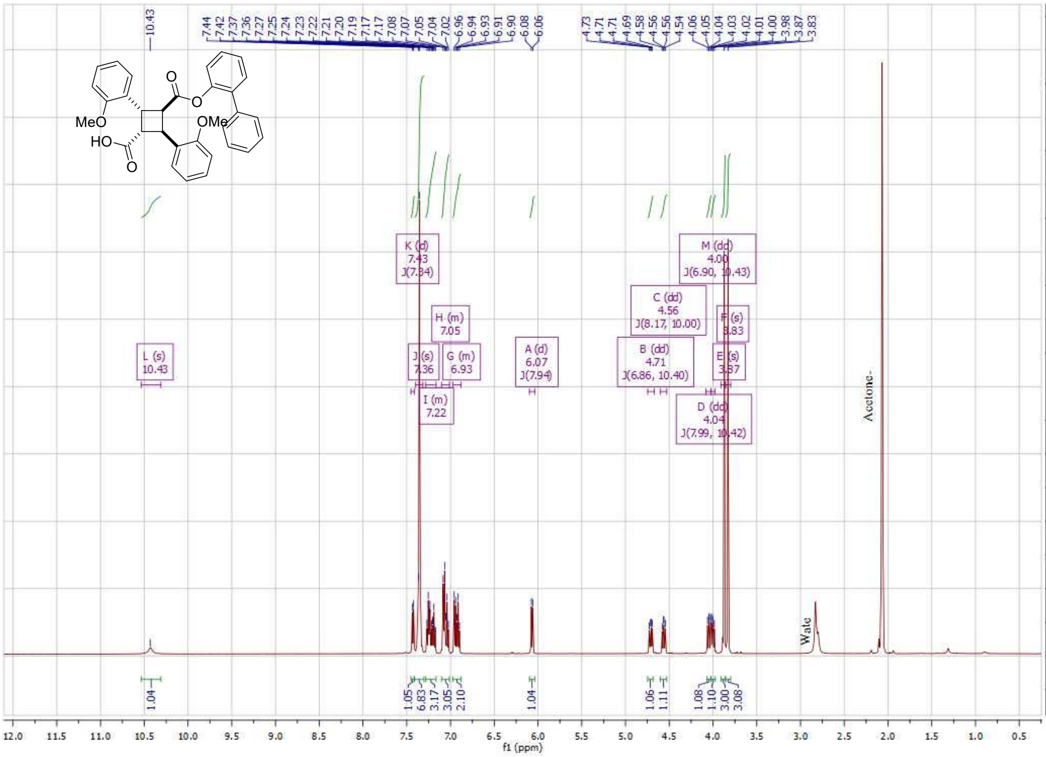
^{1}H NMR of **α-18**



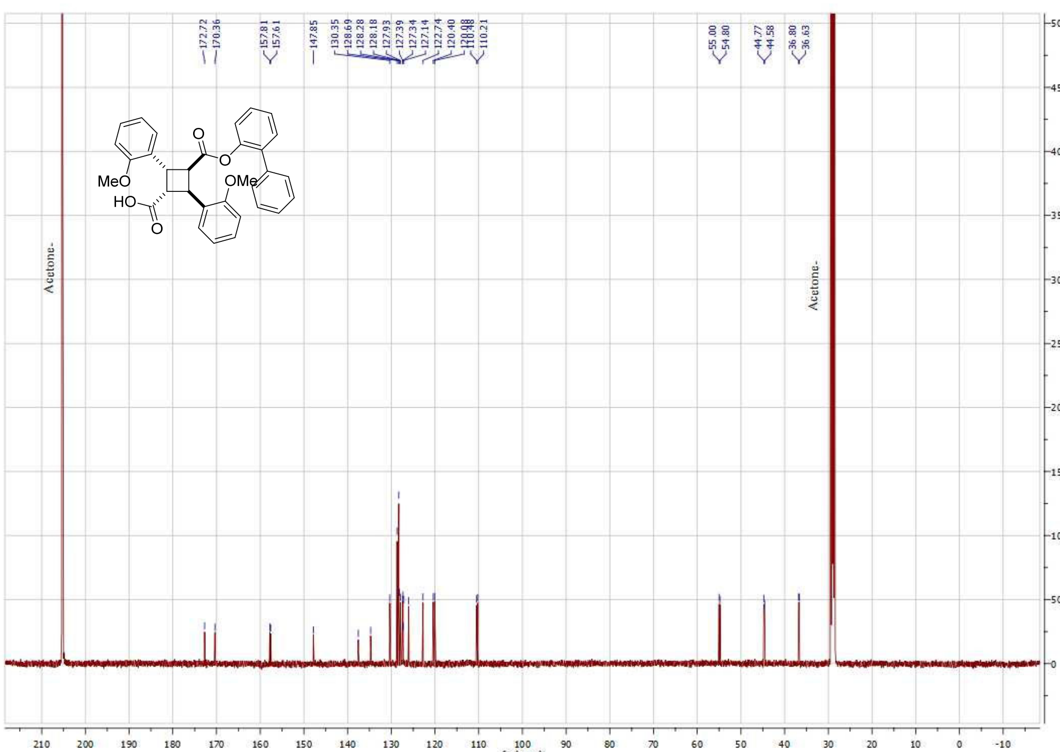
^{13}C NMR of **α-18**



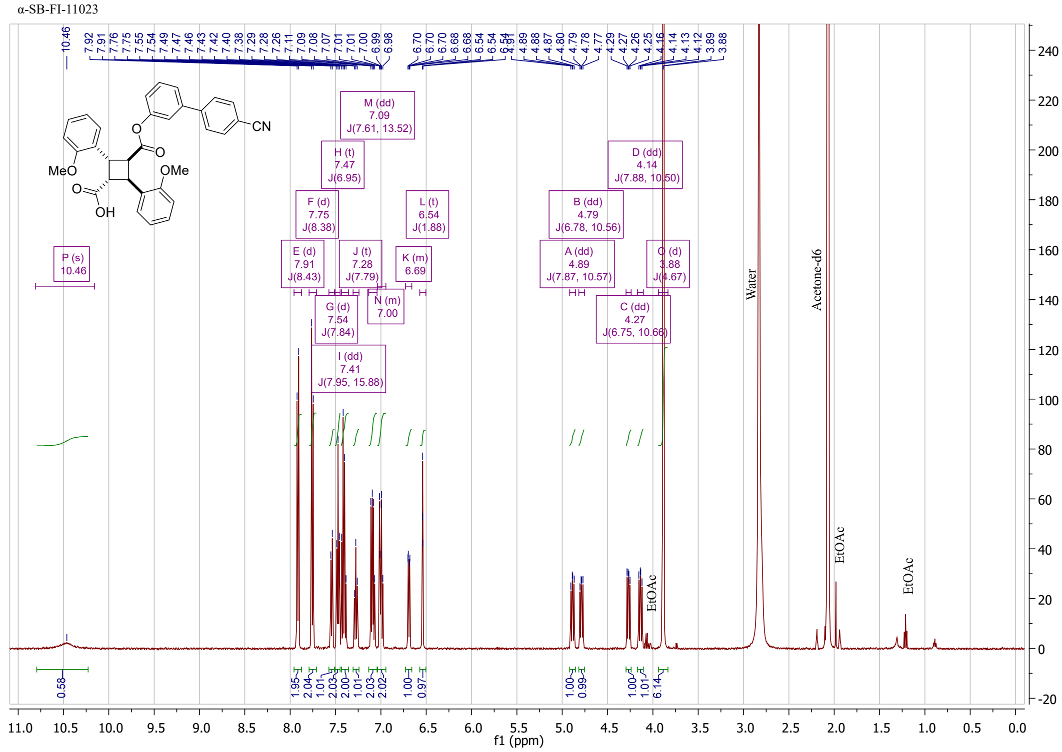
^{1}H NMR of **α-19**



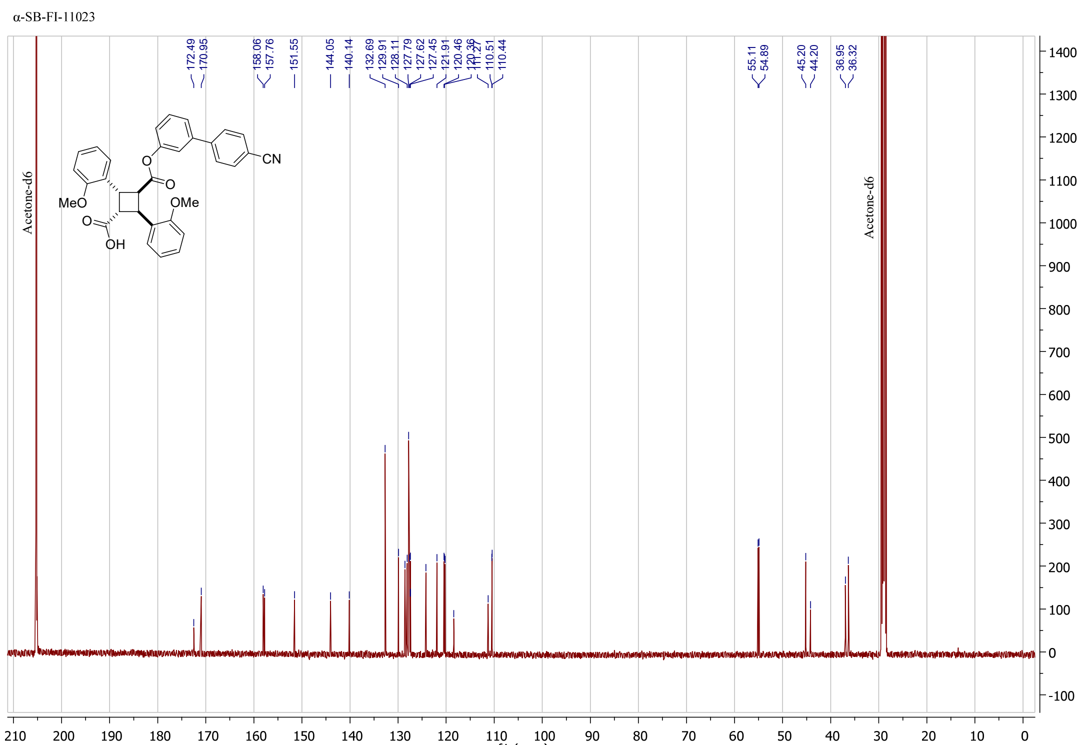
^{13}C NMR of **α-19**



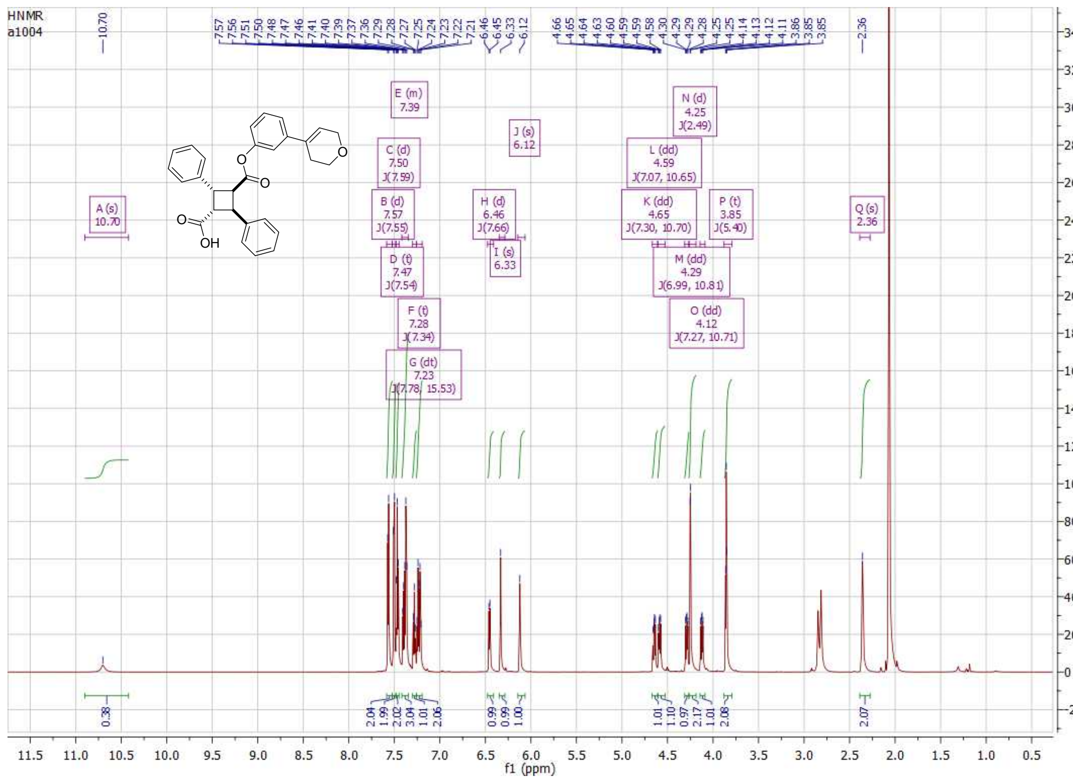
[1]H NMR of **α-20**



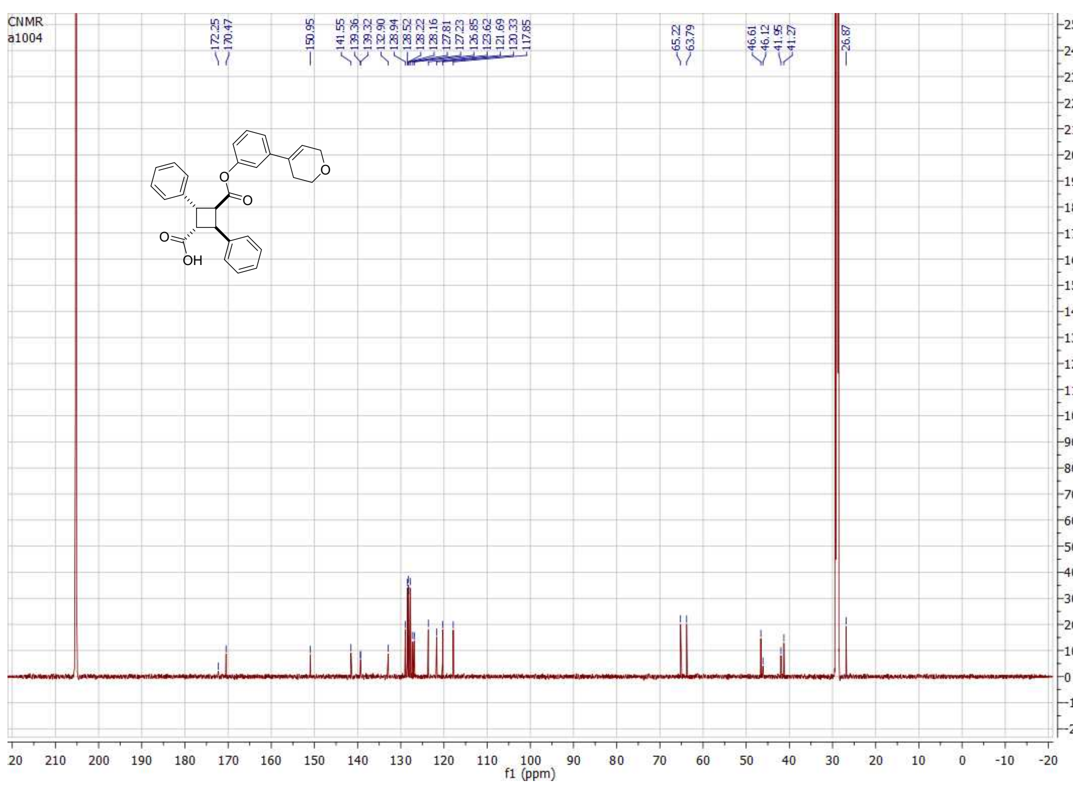
[13]C NMR of **α-20**



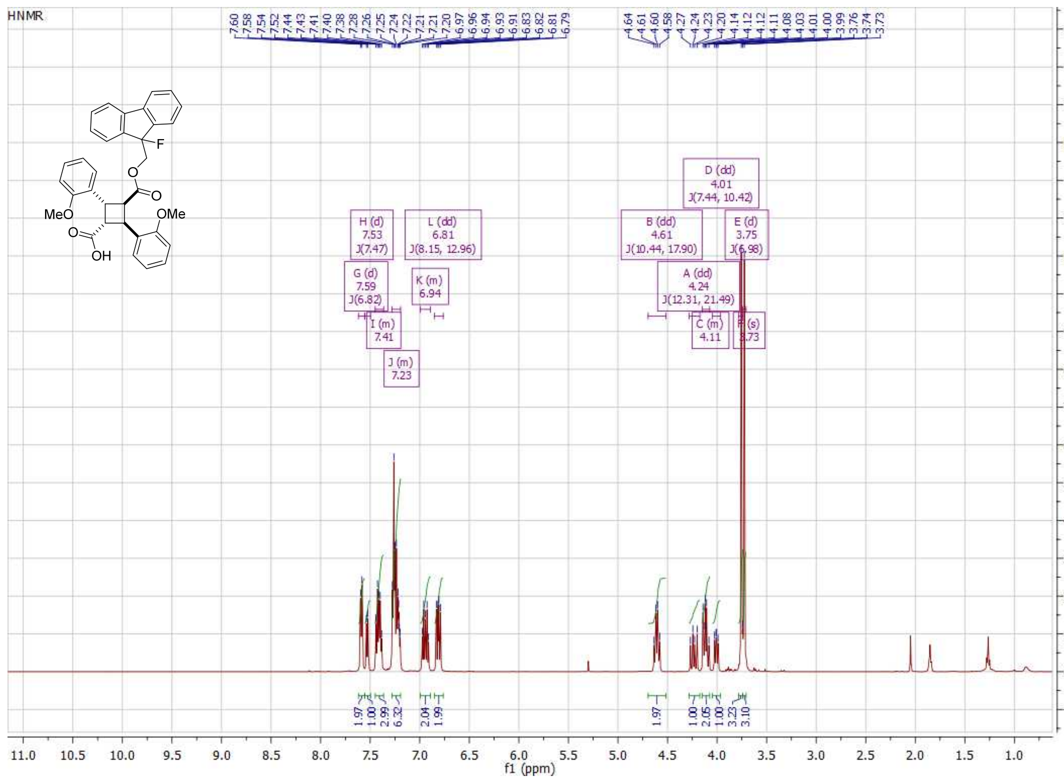
^{1}H NMR of **α-21**



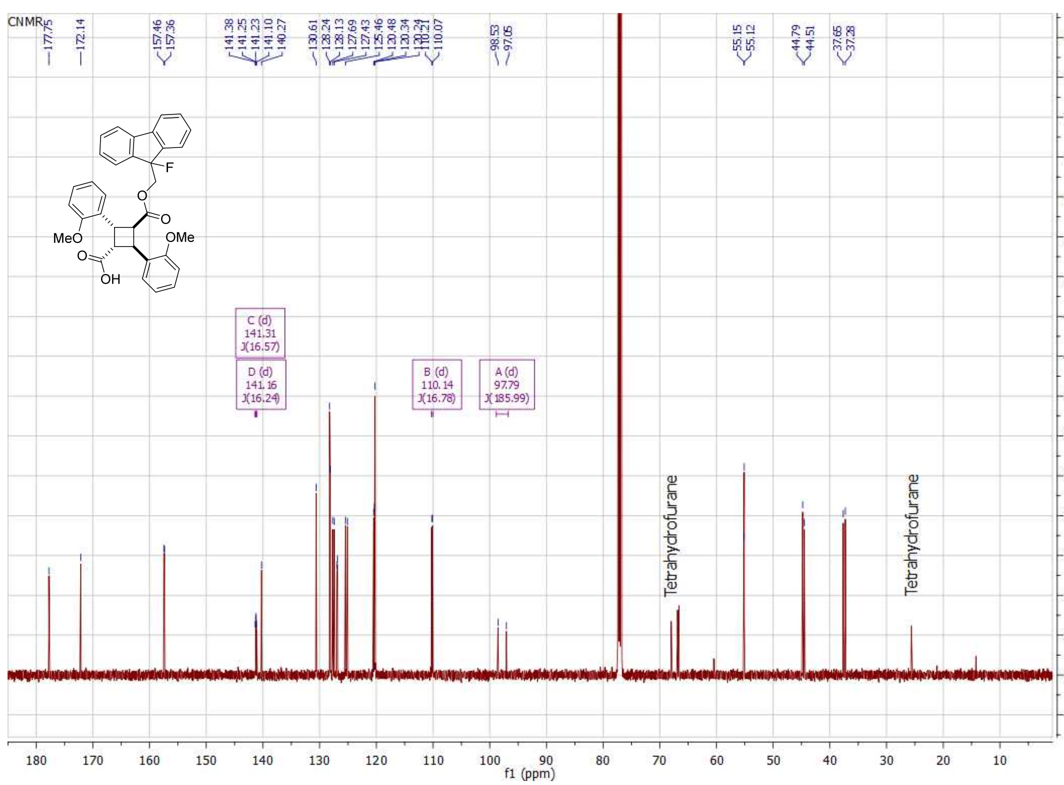
^{13}C NMR of **α-21**



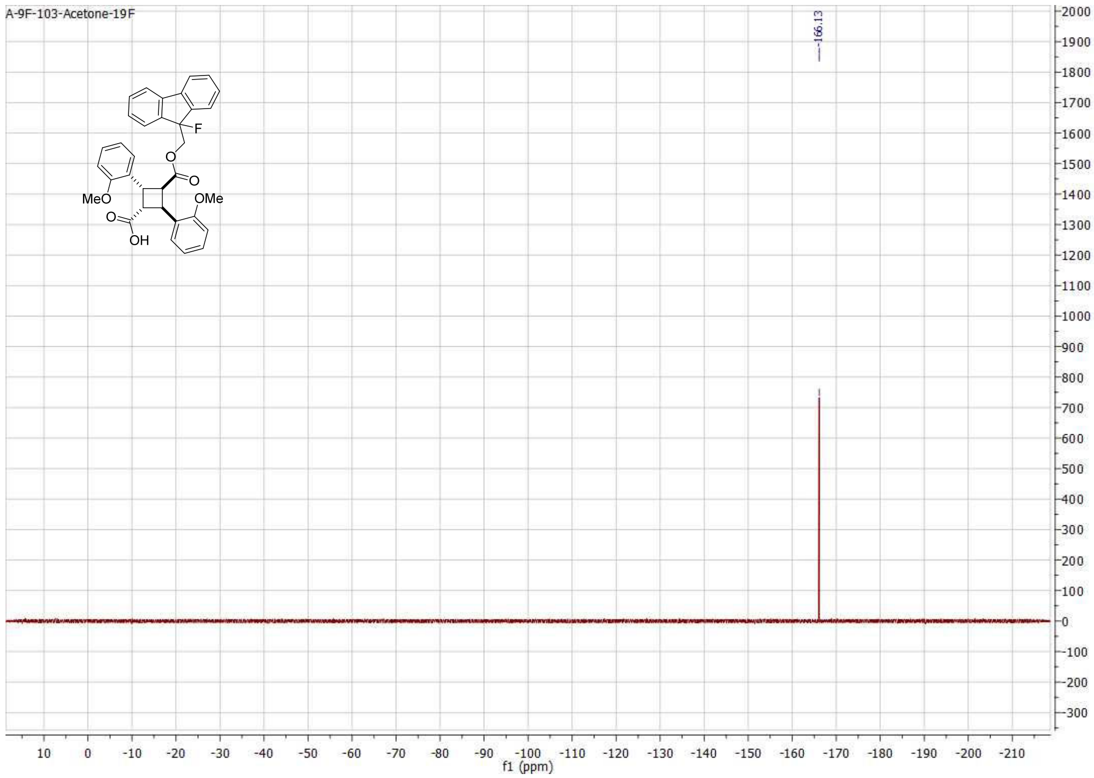
^{1}H NMR of **α-22**



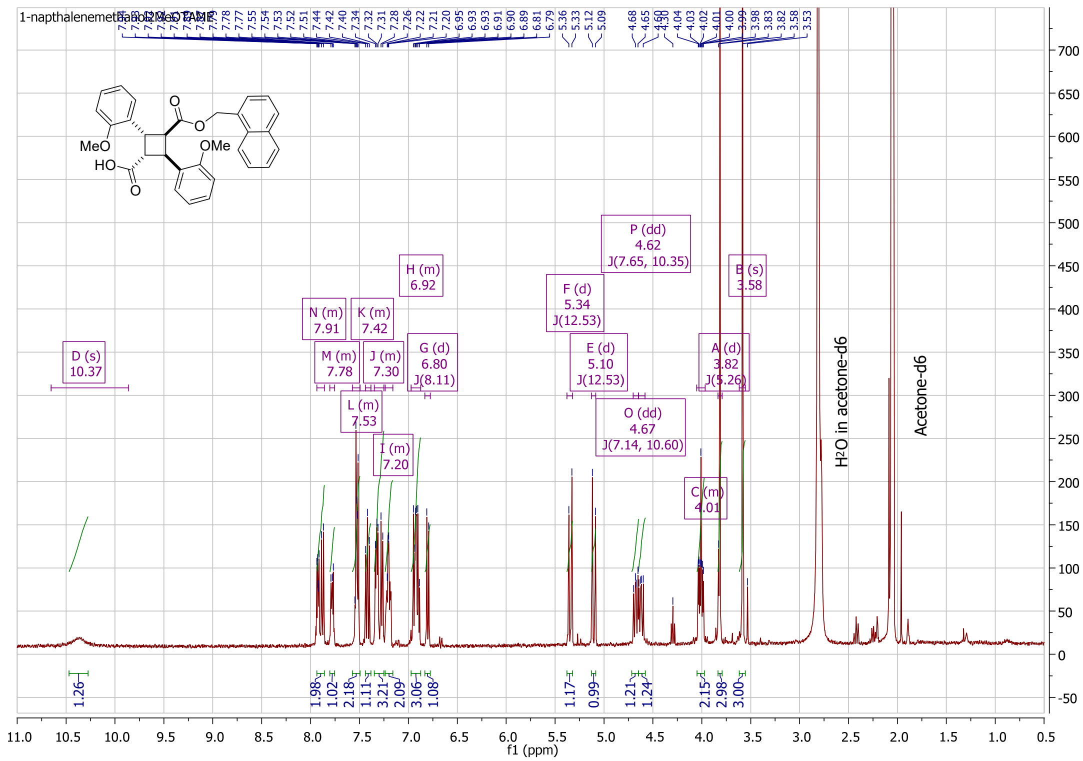
^{13}C NMR of **α-22**



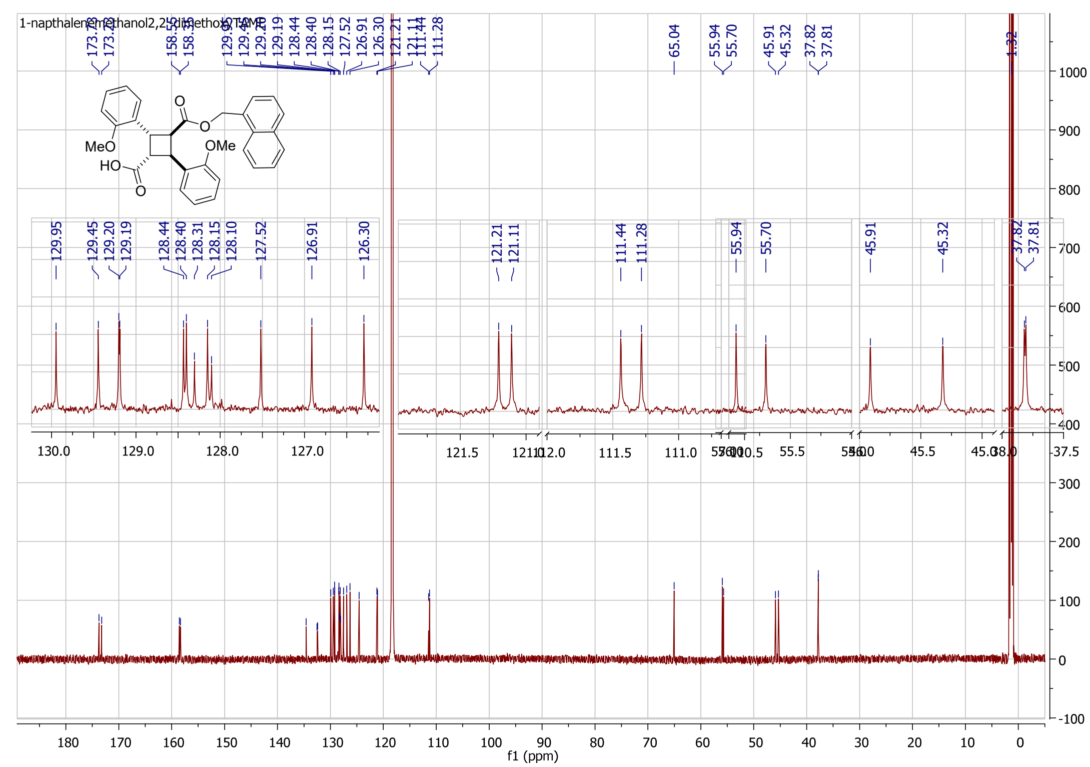
^{19}FNMR of **α-22**



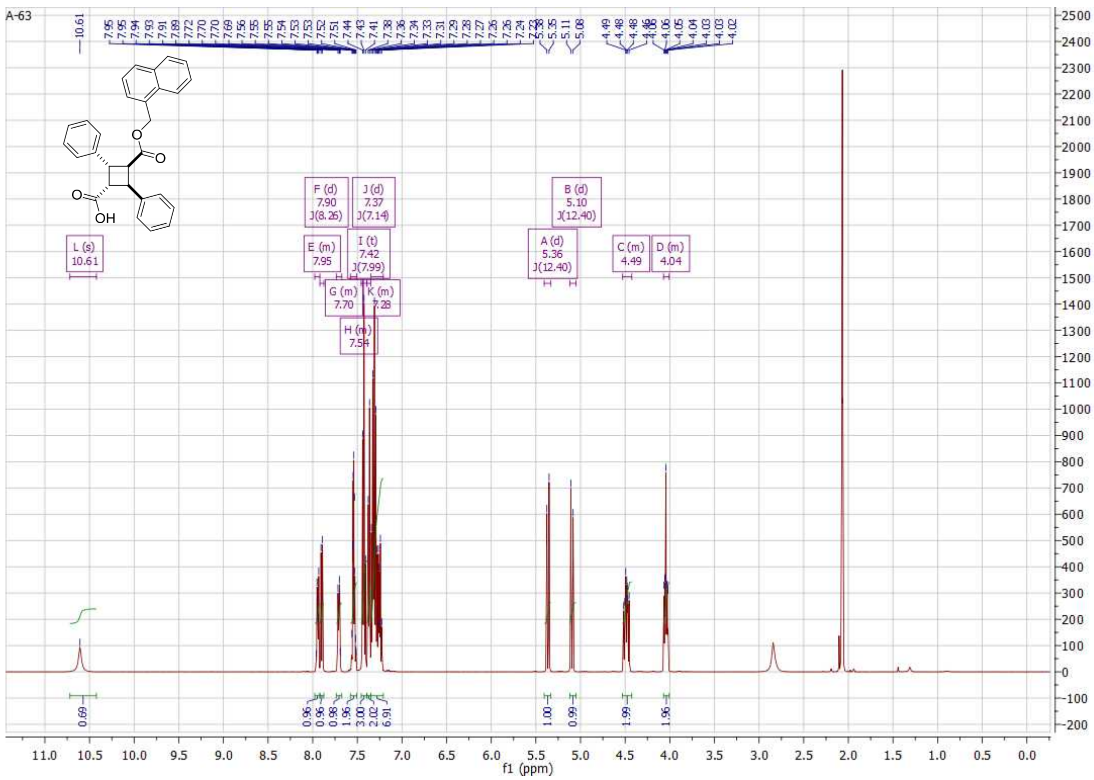
[1]H NMR of **α-23**



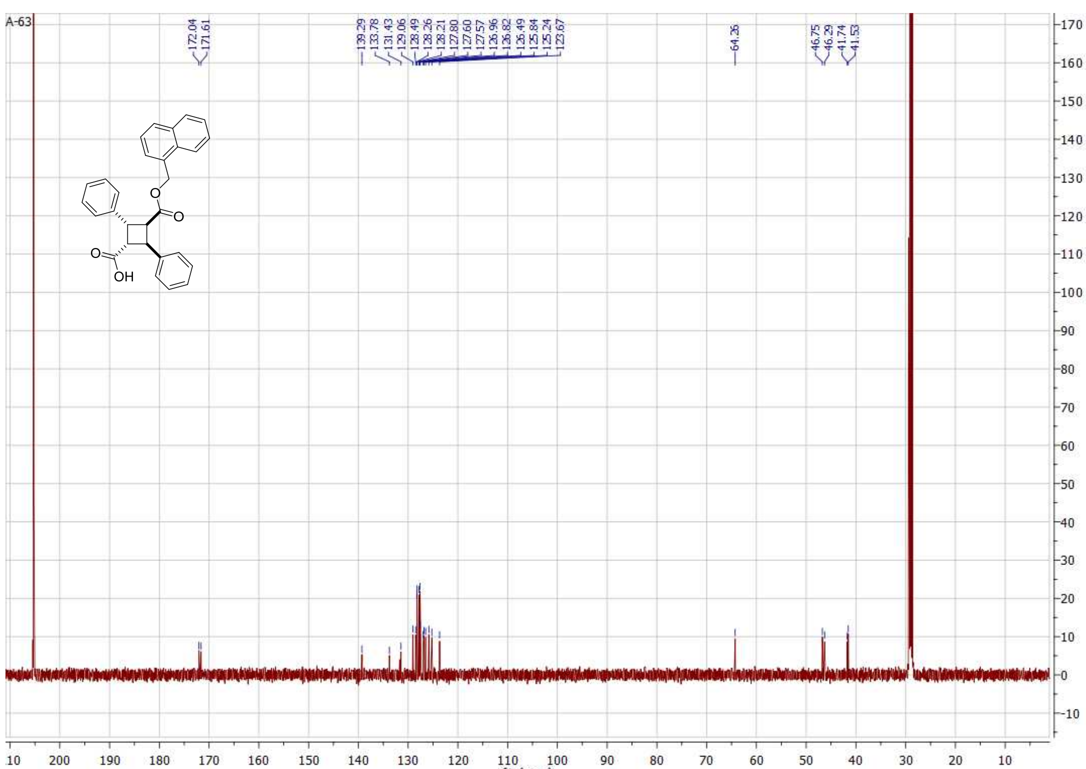
[13]C NMR of **α-23**



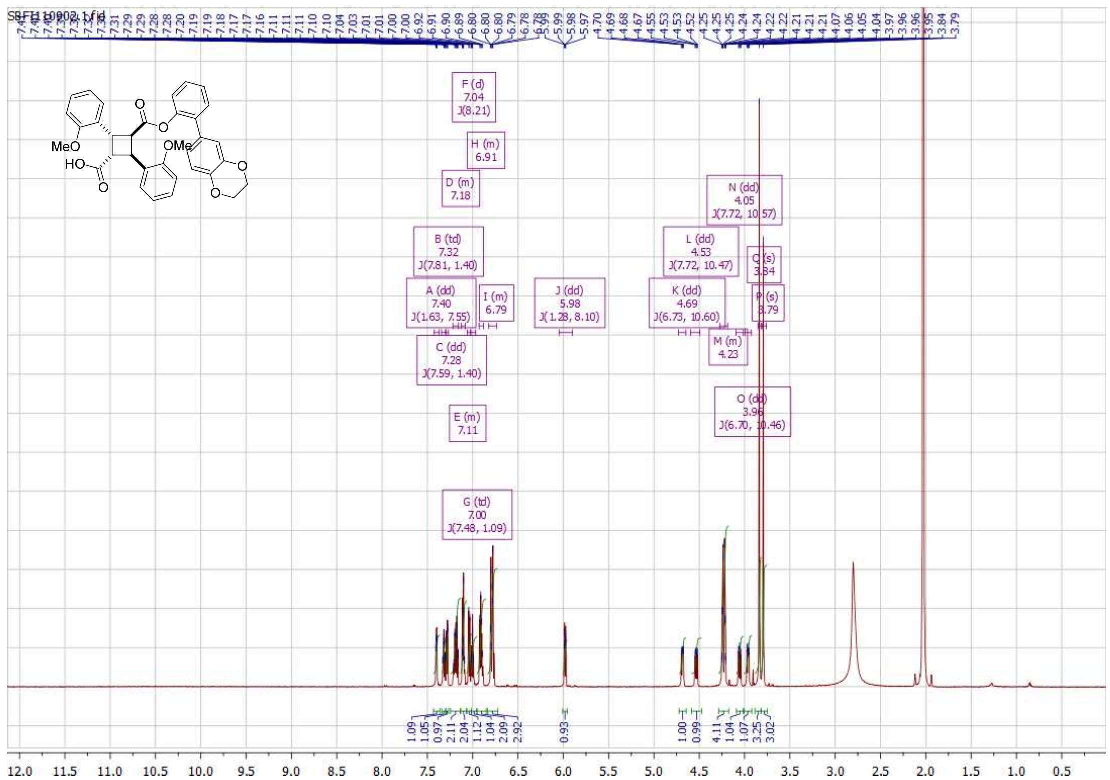
^{1}H NMR of **α-24**



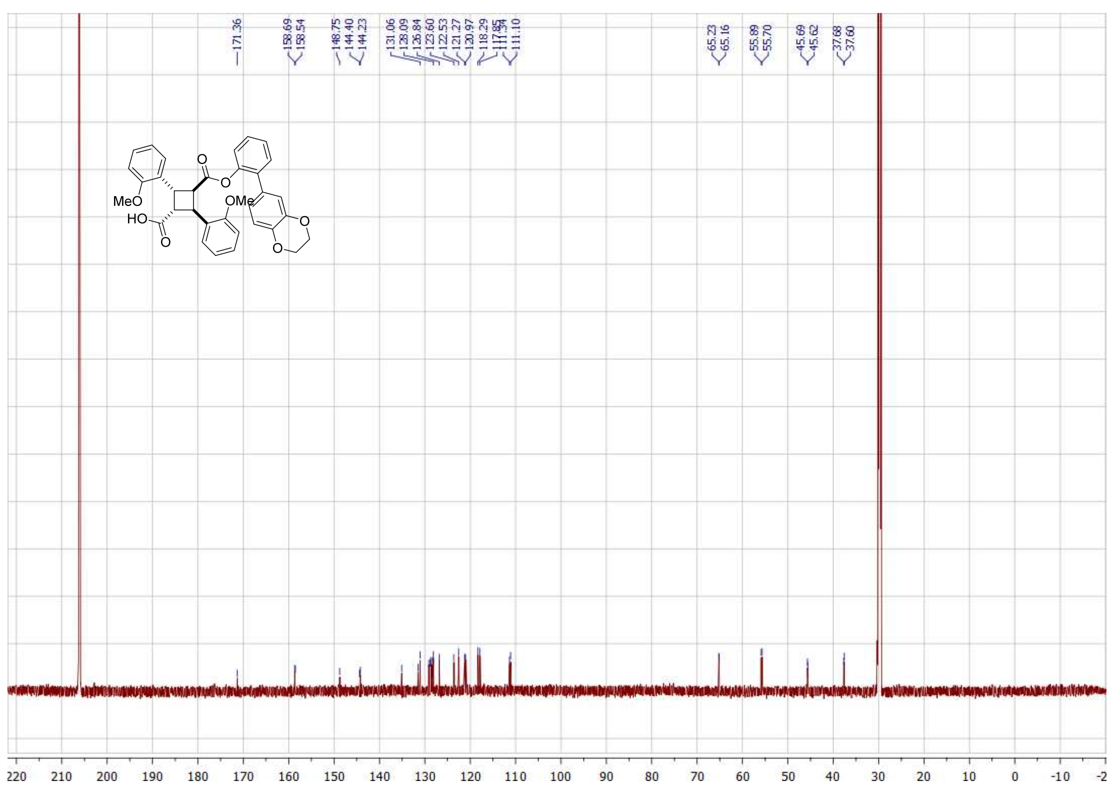
^{13}C NMR of **α-24**



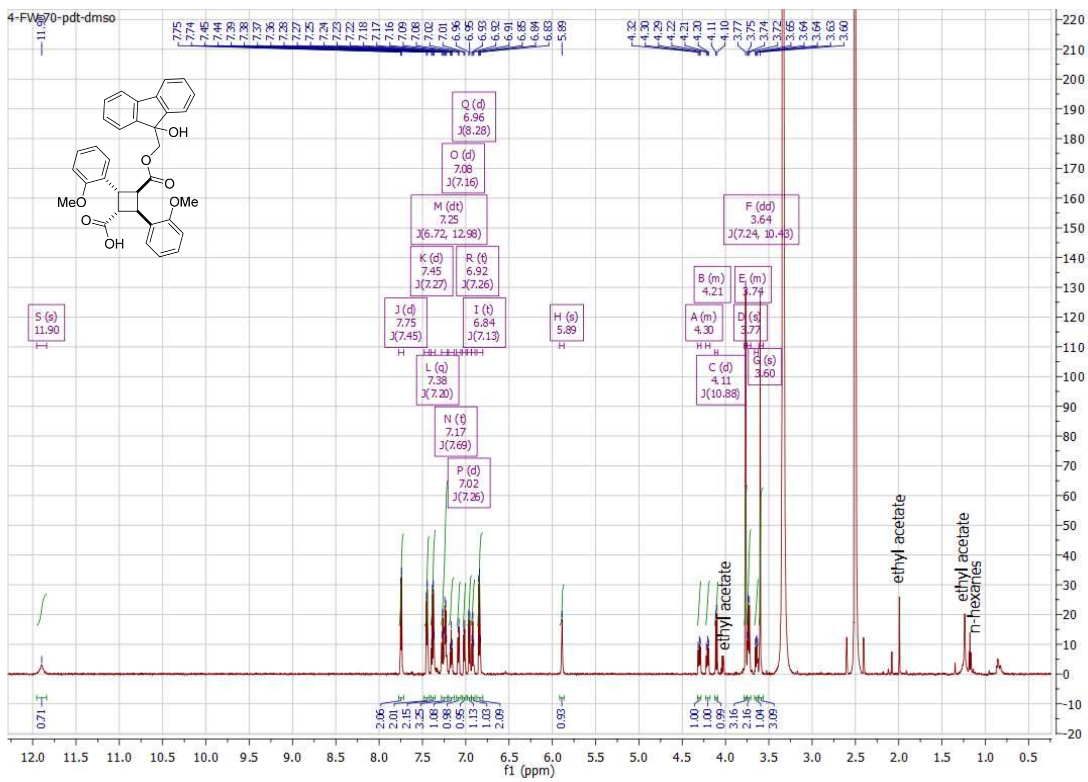
[1]H NMR of **α-25**



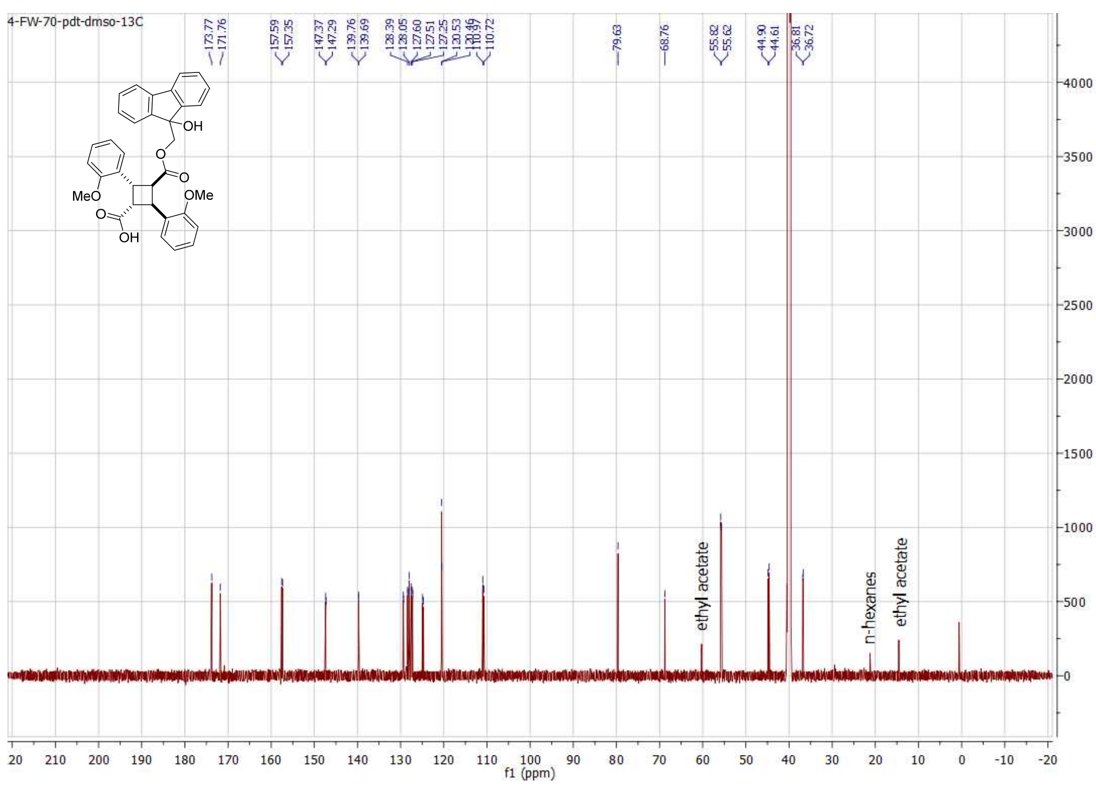
[13]C NMR of **α-25**



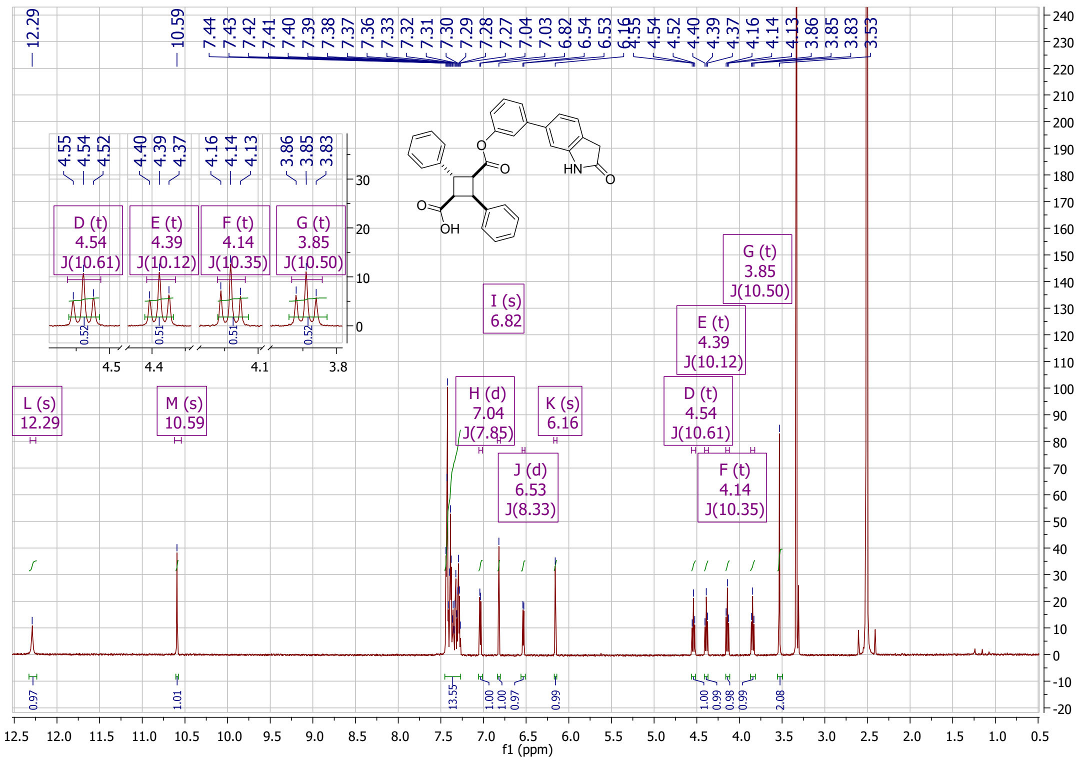
^{1}H NMR of **α-26**



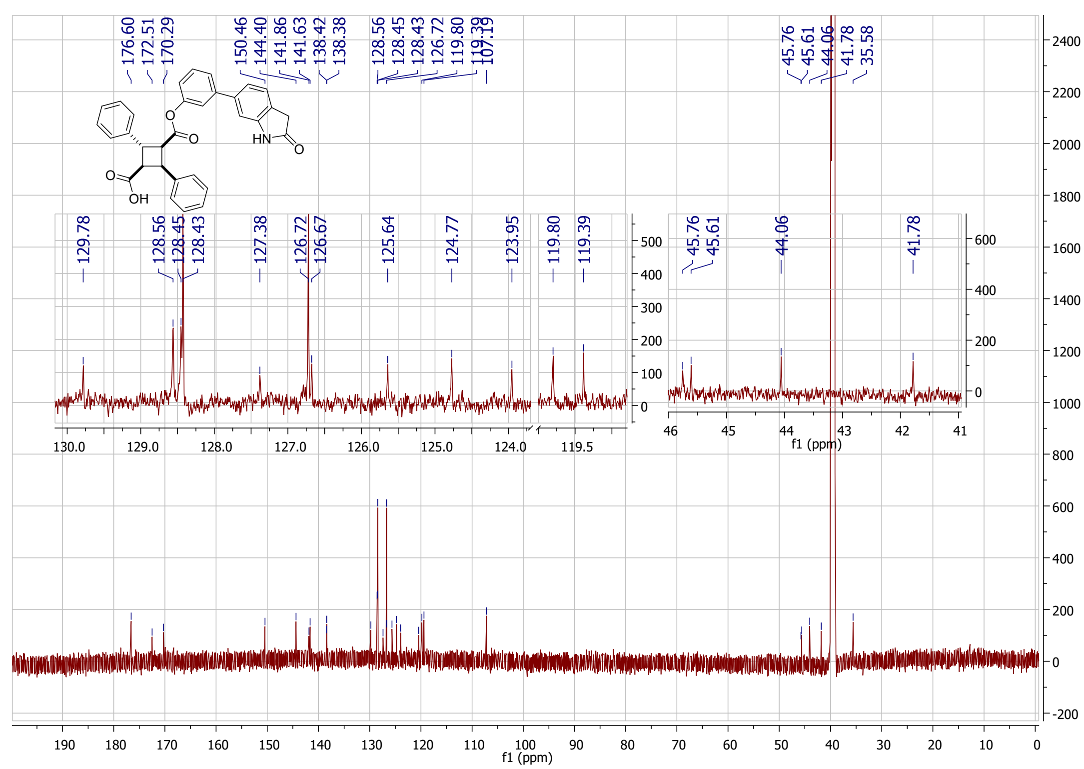
^{13}C NMR of **α-26**



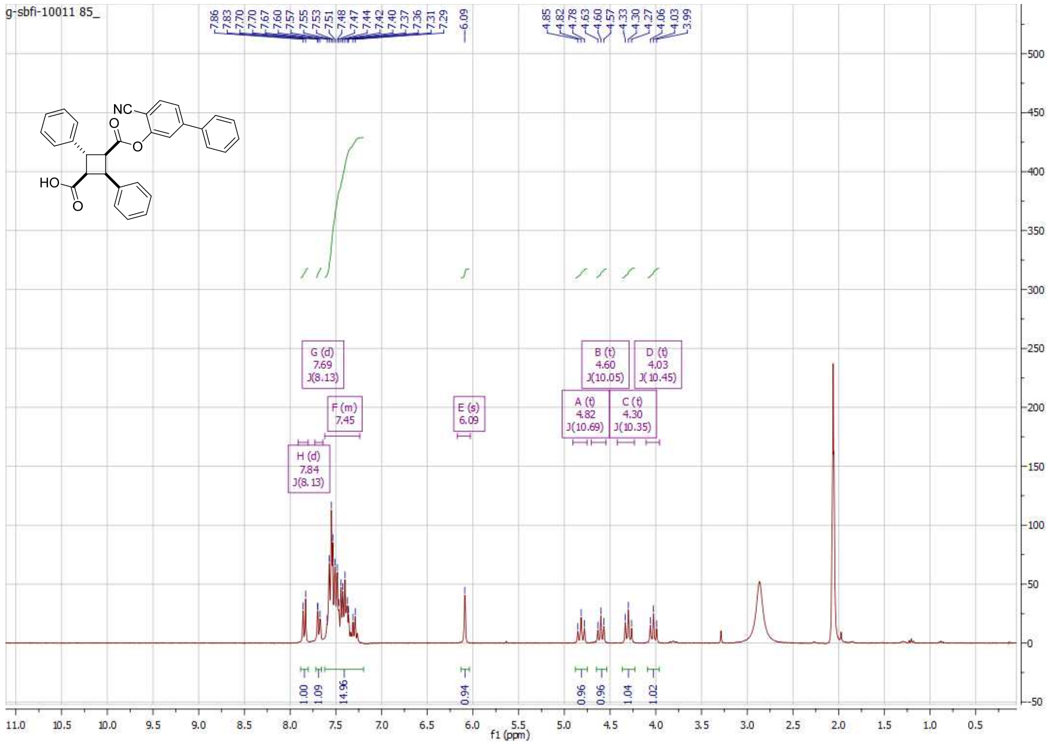
[1]H NMR of **γ-1**



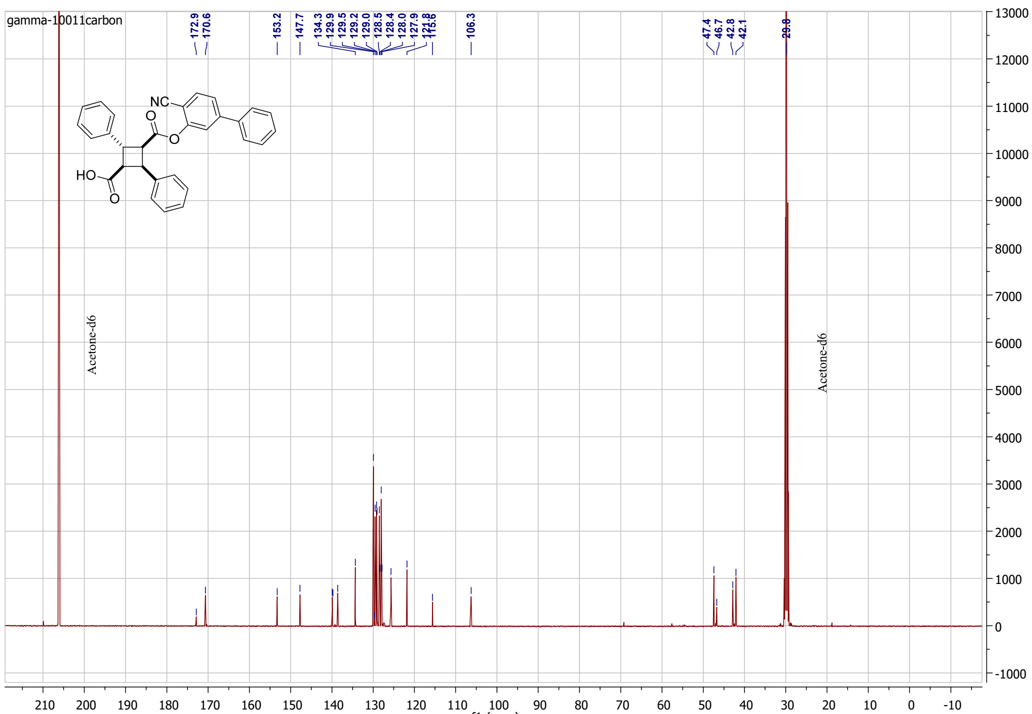
[13]C NMR of **γ-1**



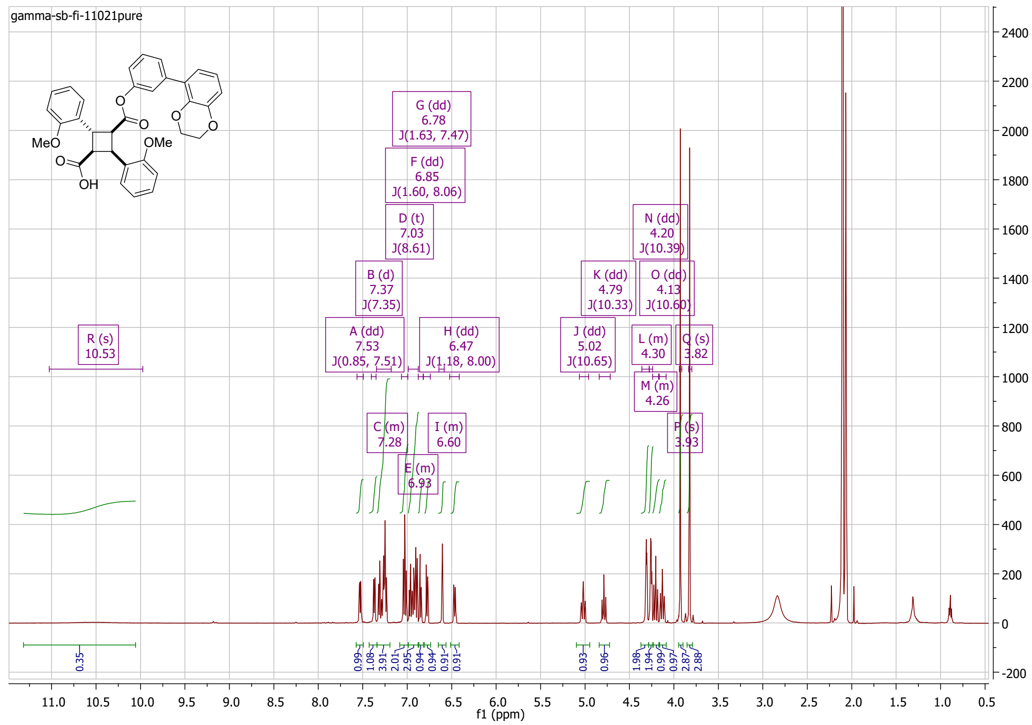
[1]H NMR of **γ-3**



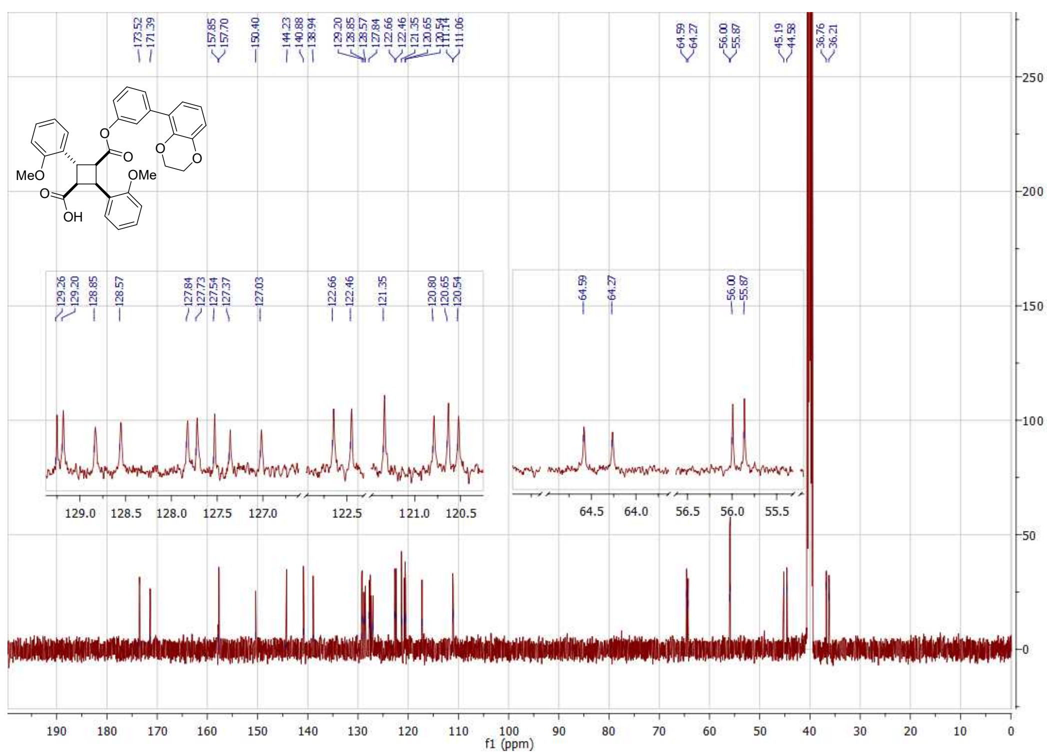
[13]C NMR of **γ-3**



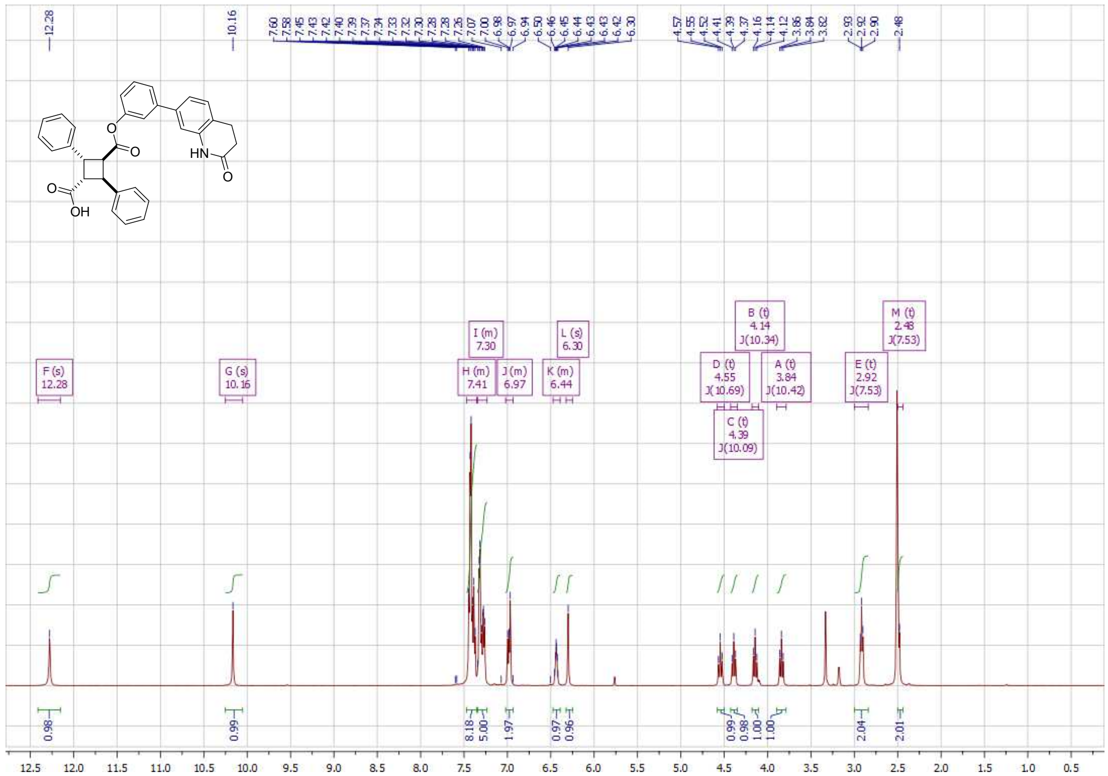
^{1}H NMR of **γ-6**



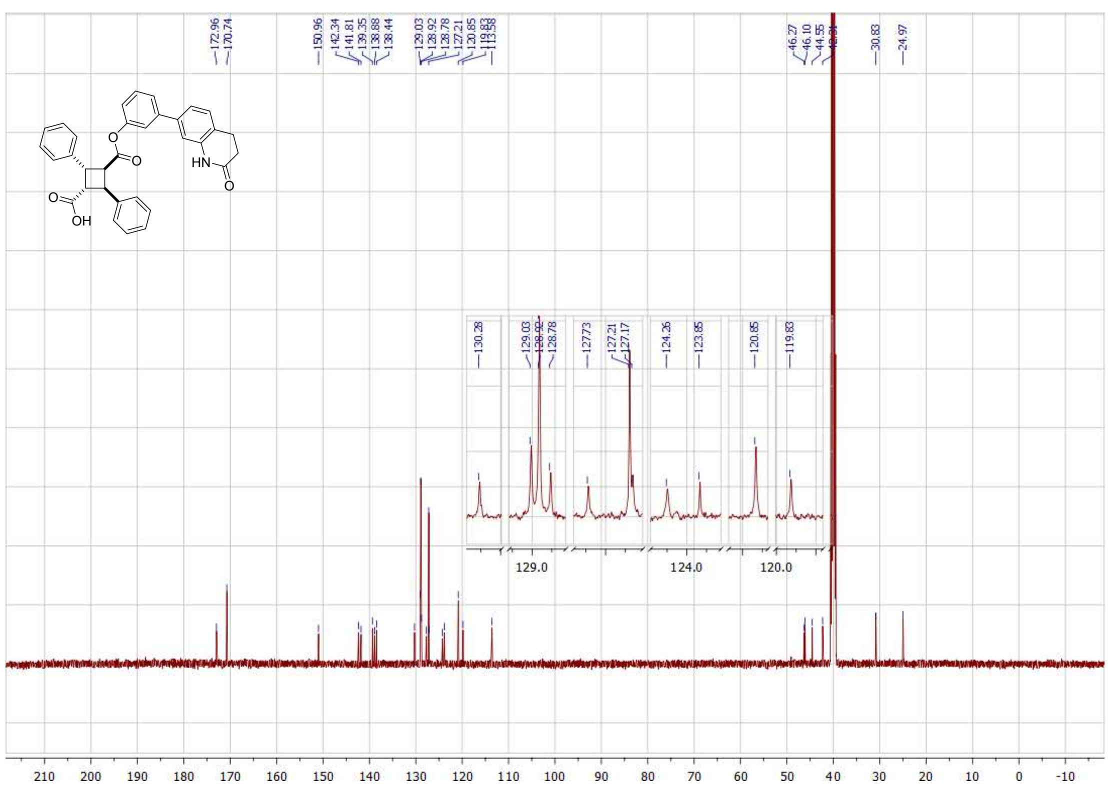
^{13}C NMR of **γ-6**



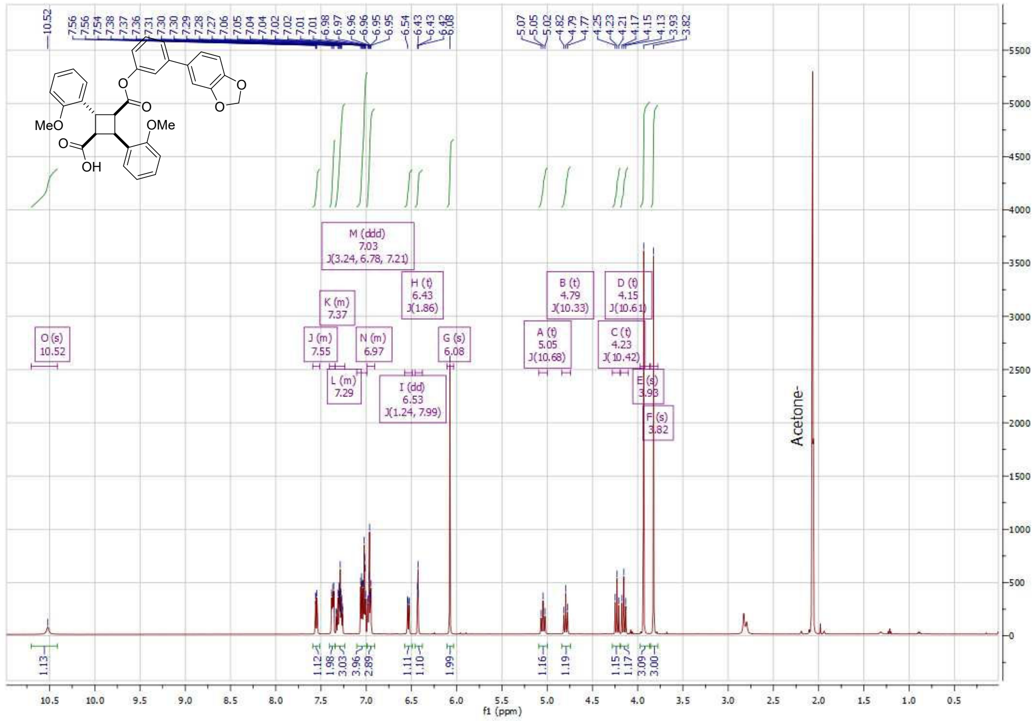
^{1}H NMR of **γ-8**



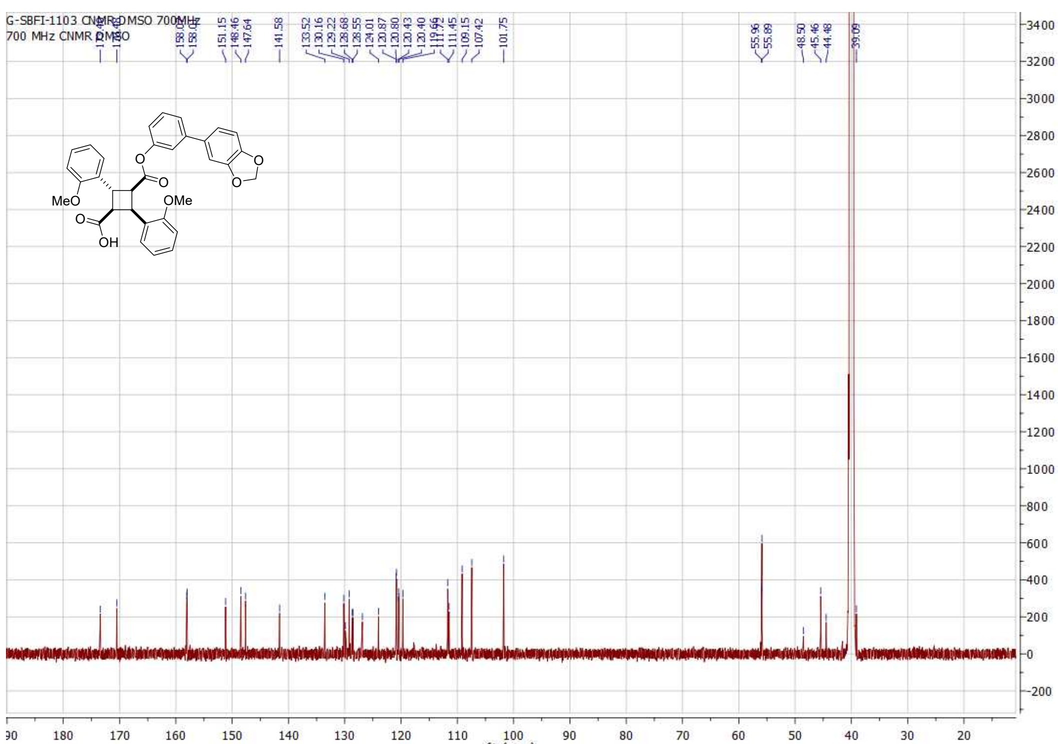
^{13}C NMR of **γ-8**



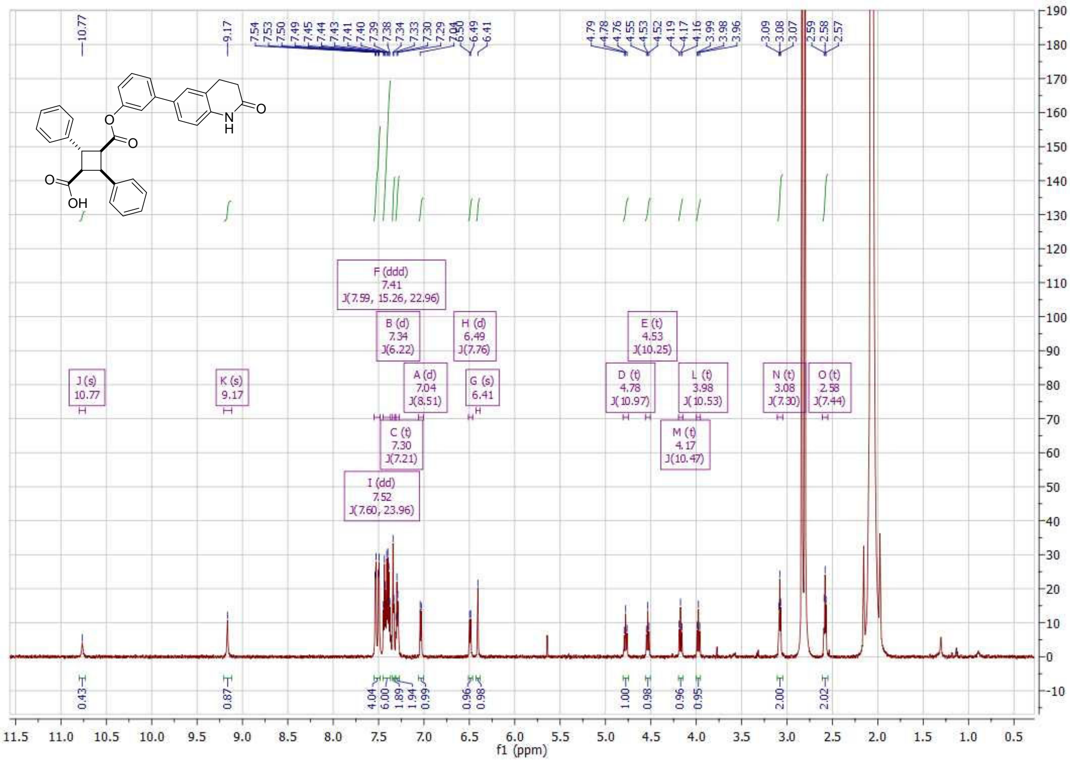
^{1}H NMR of **γ-9**



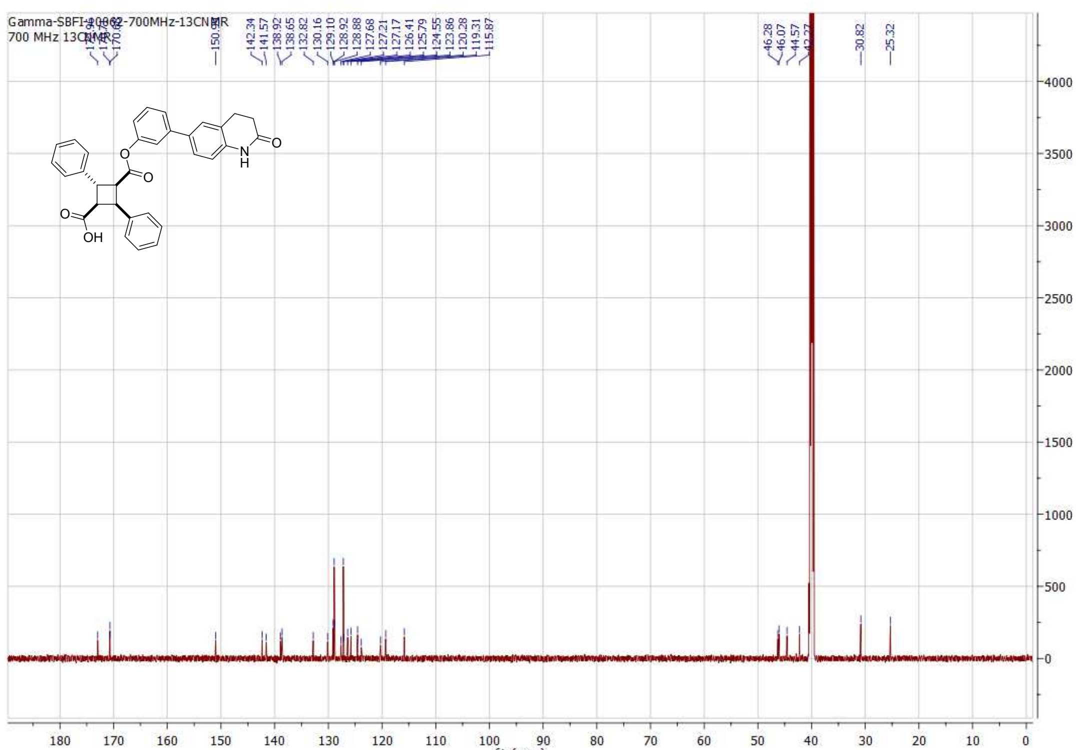
^{13}C NMR of **γ-9**



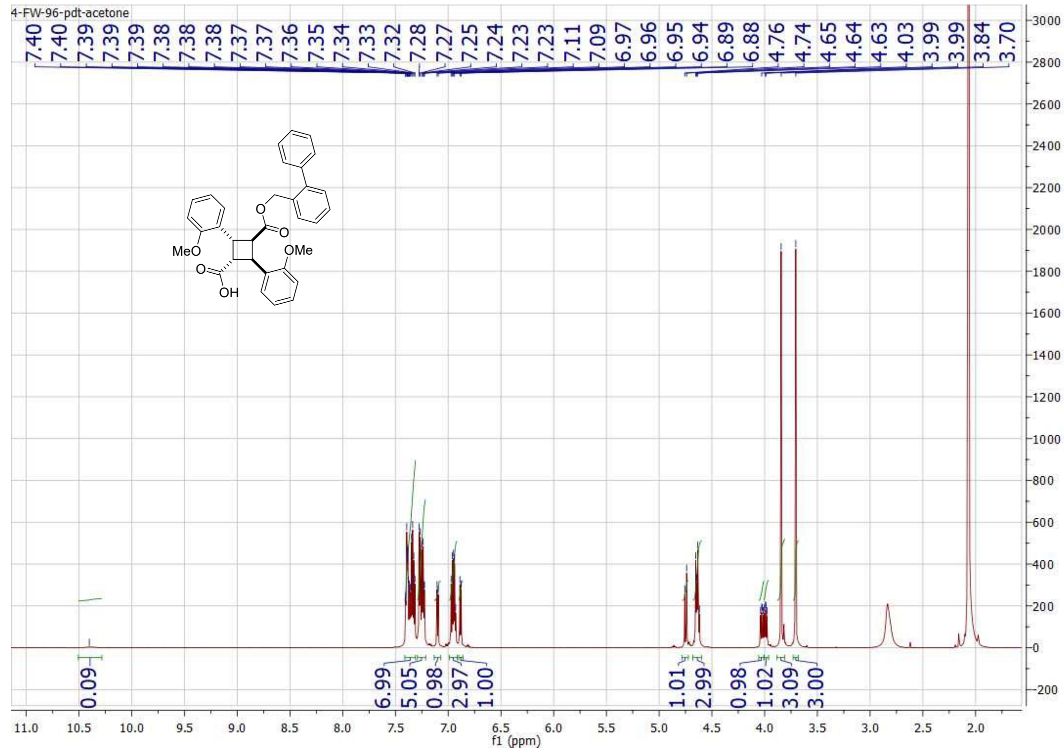
^{1}H NMR of **γ-10**



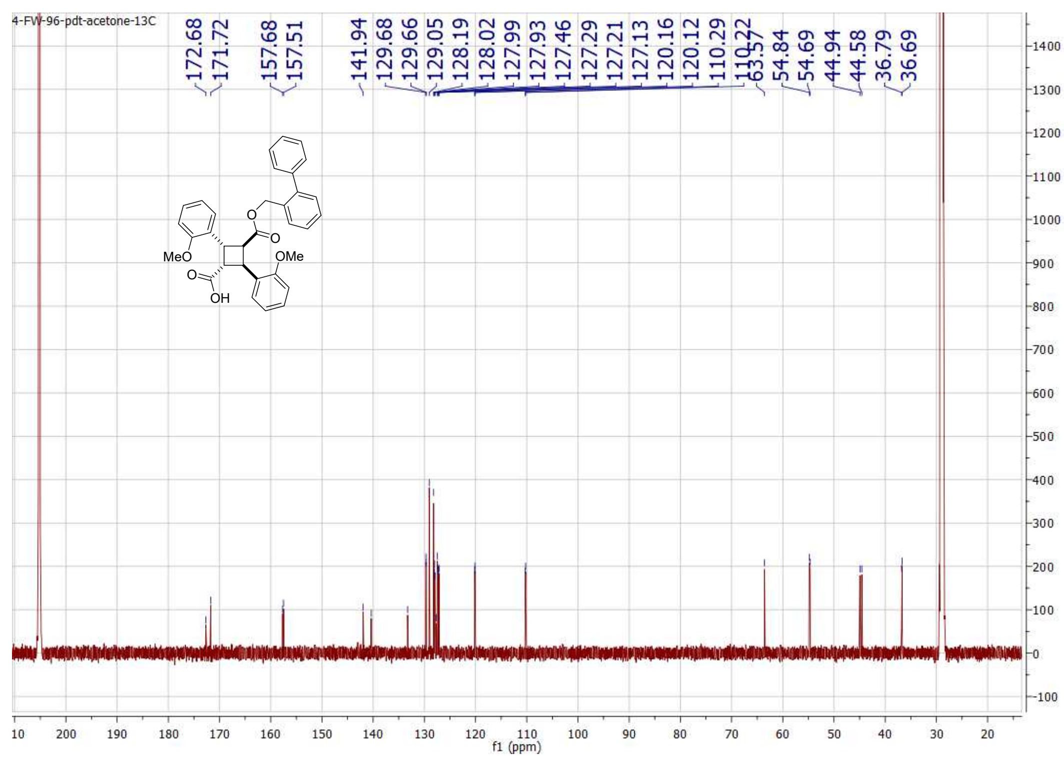
^{13}C NMR of **γ-10**



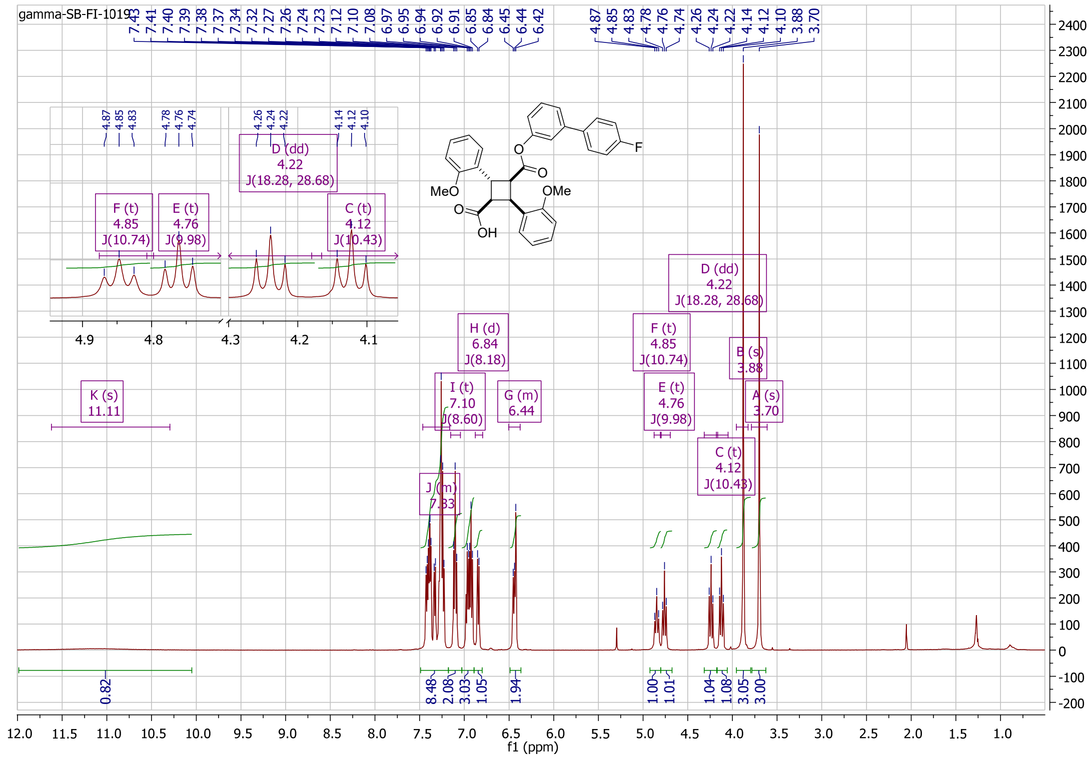
^{1}H NMR of **γ-12**



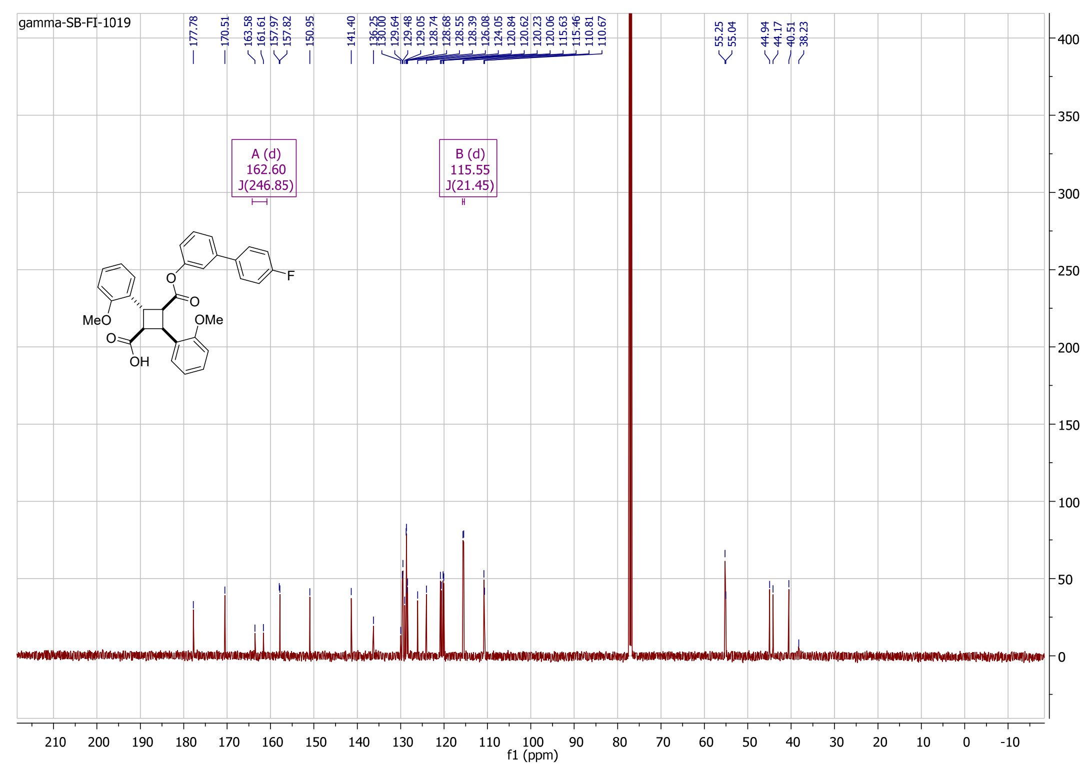
^{13}C NMR of **γ-12**



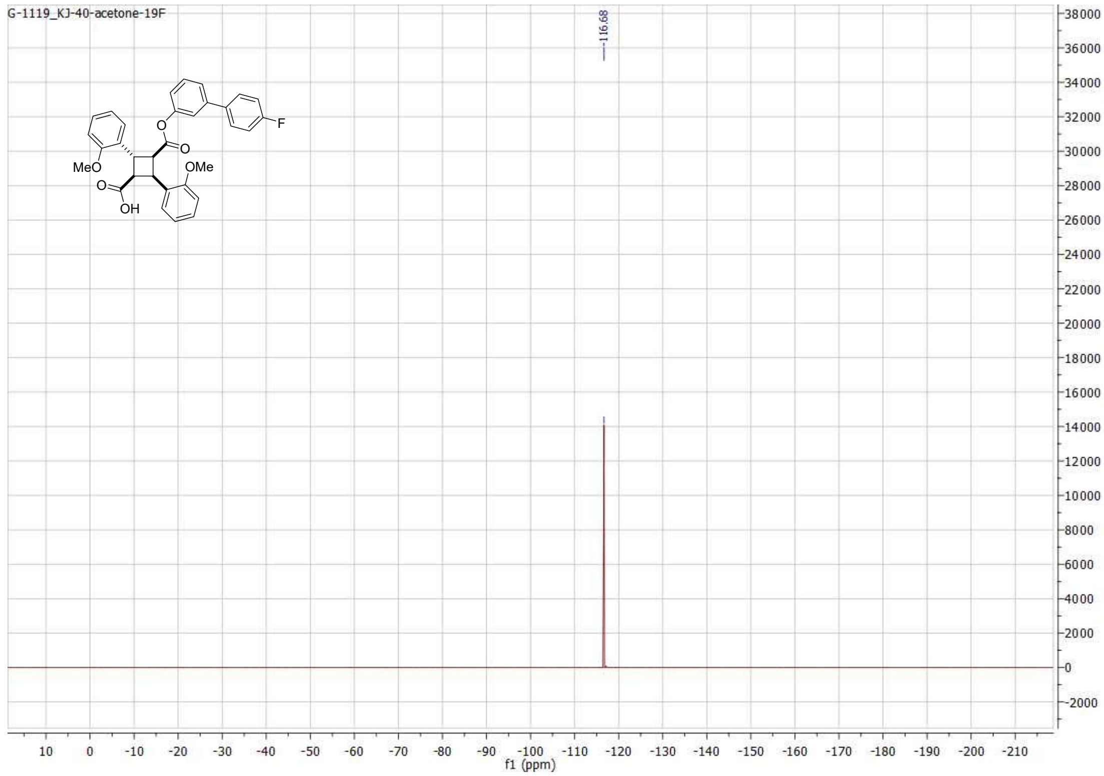
[1]H NMR of **γ-13**



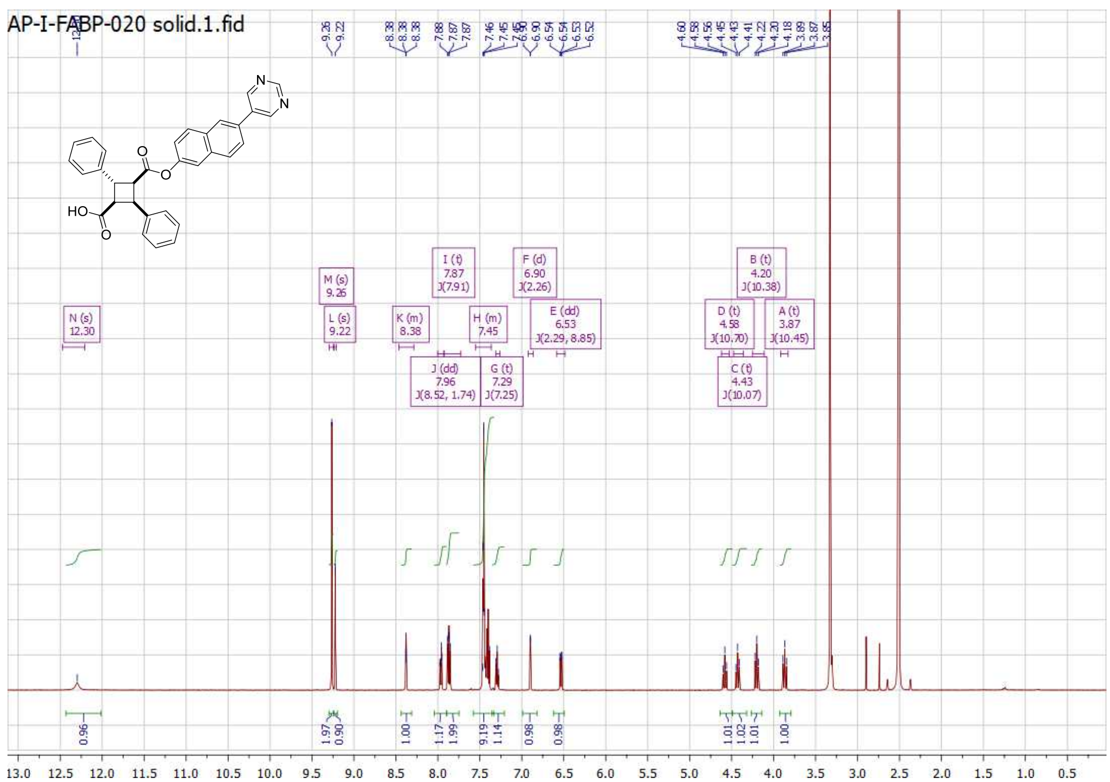
[13]C NMR of **γ-13**



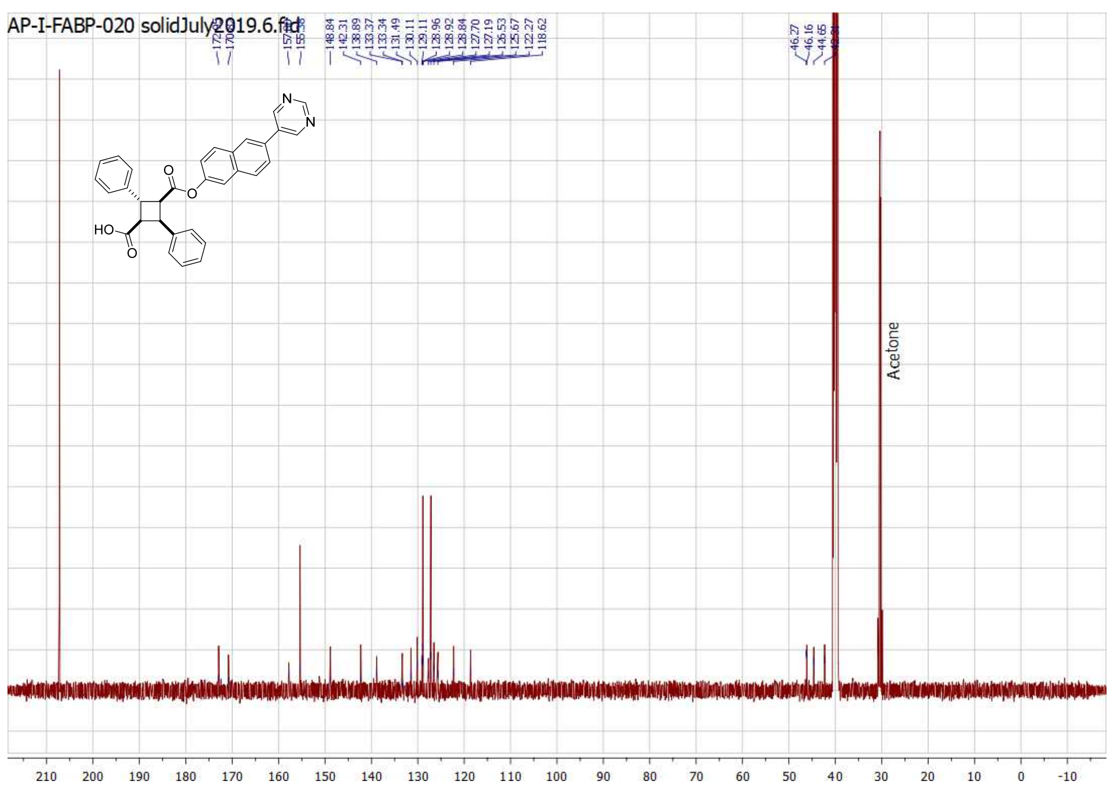
^{19}F NMR of **γ-13**



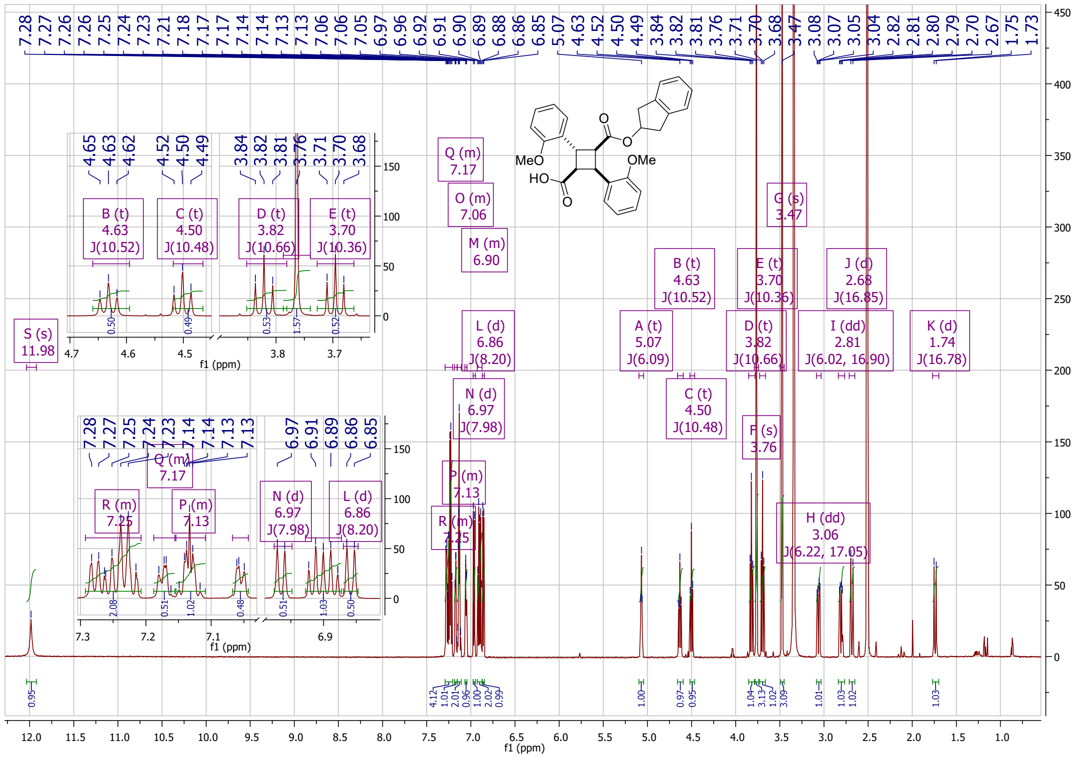
^{1}H NMR of **γ-14**



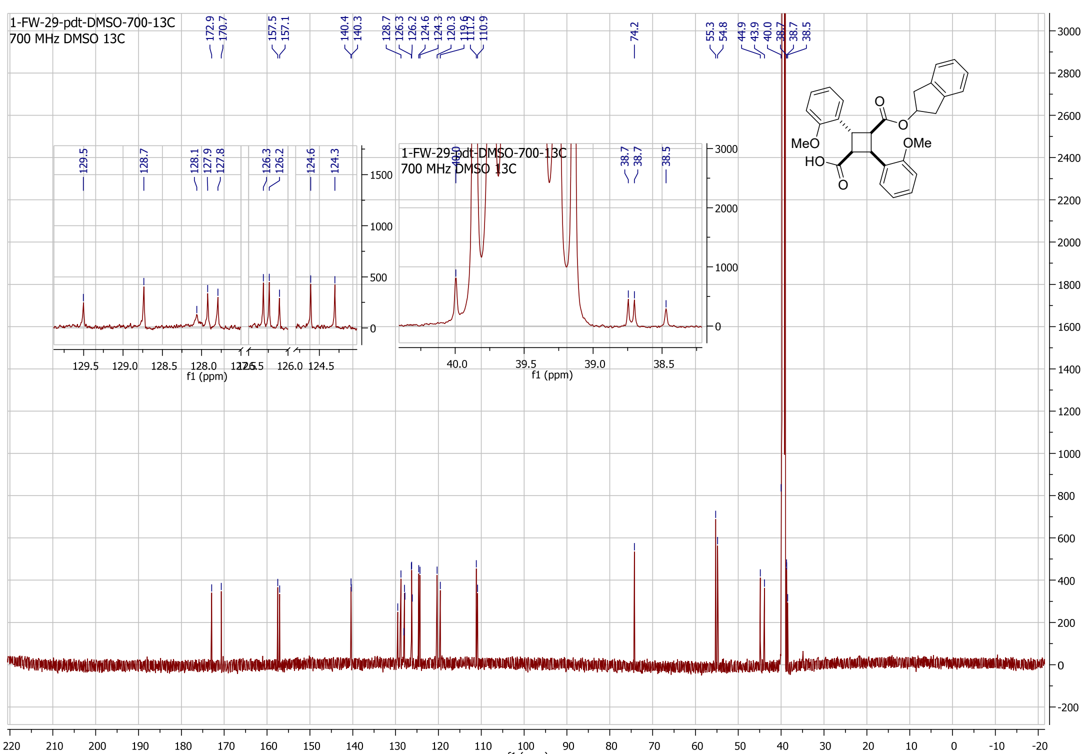
^{13}C NMR of **γ-14**



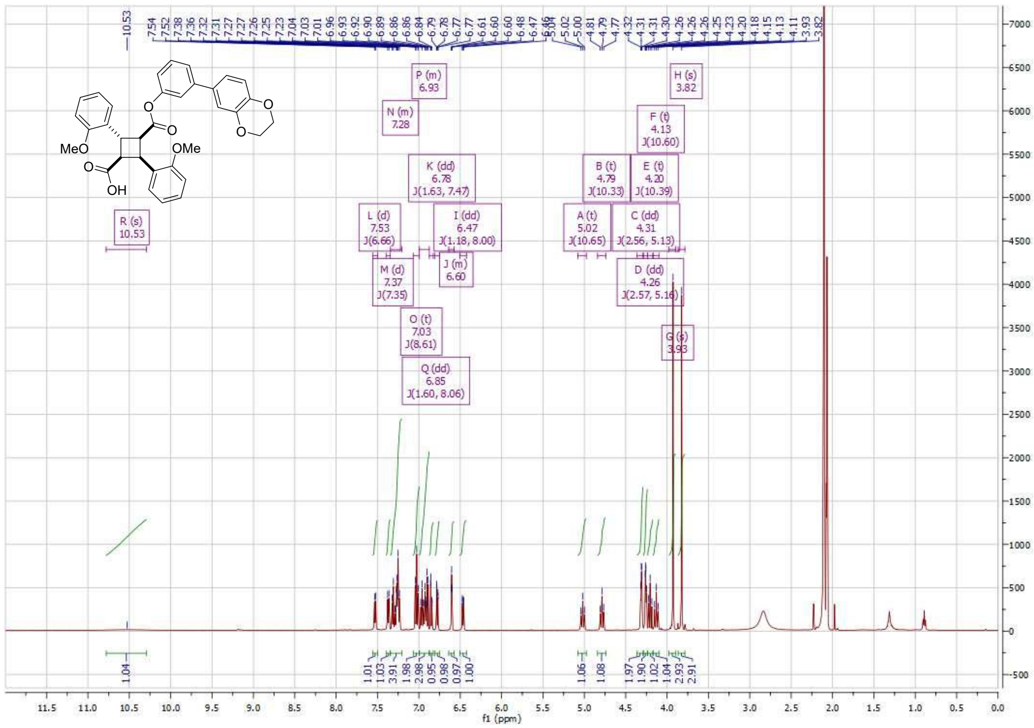
^{1}H NMR of **γ-15**



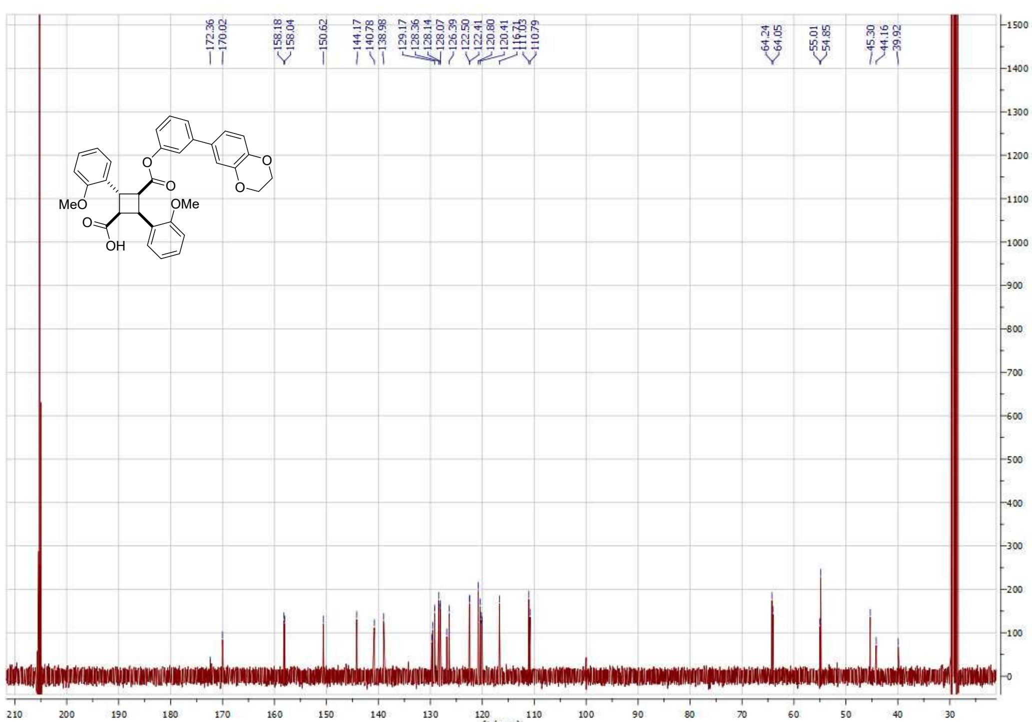
^{13}C NMR of **γ-15**



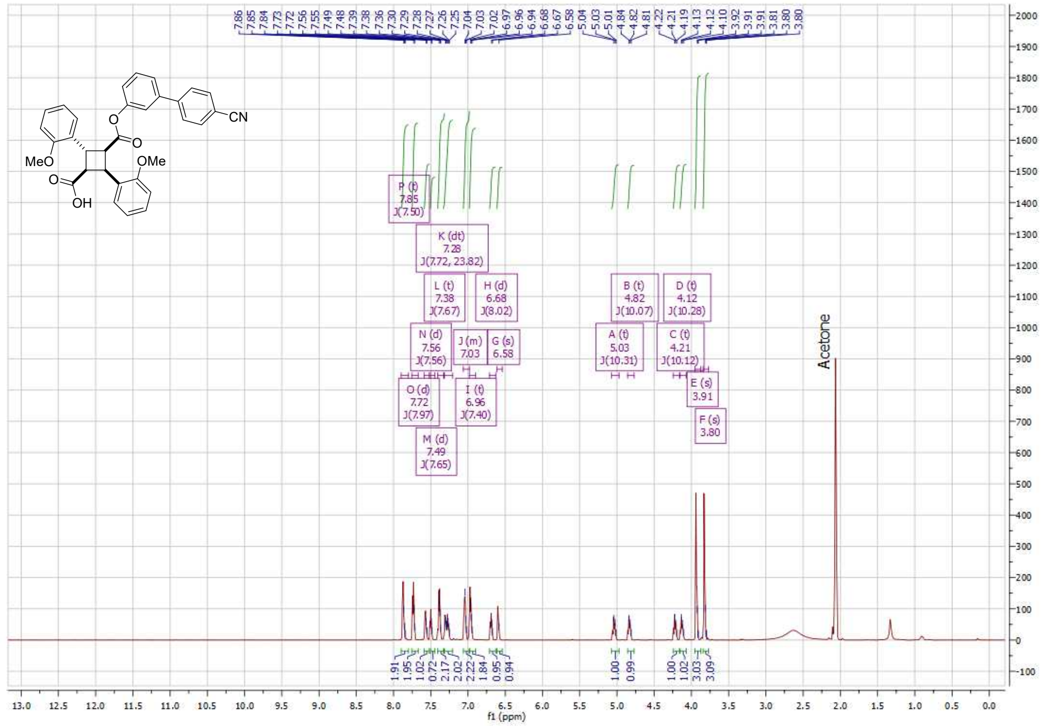
[1]H NMR of **γ-16**



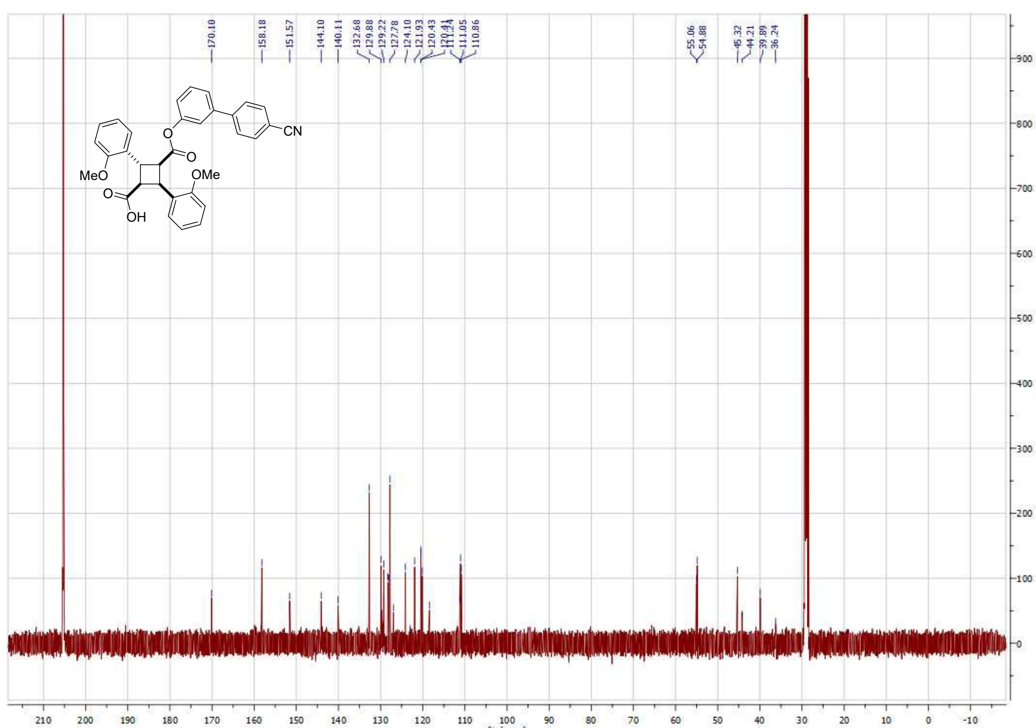
[13]C NMR of **γ-16**



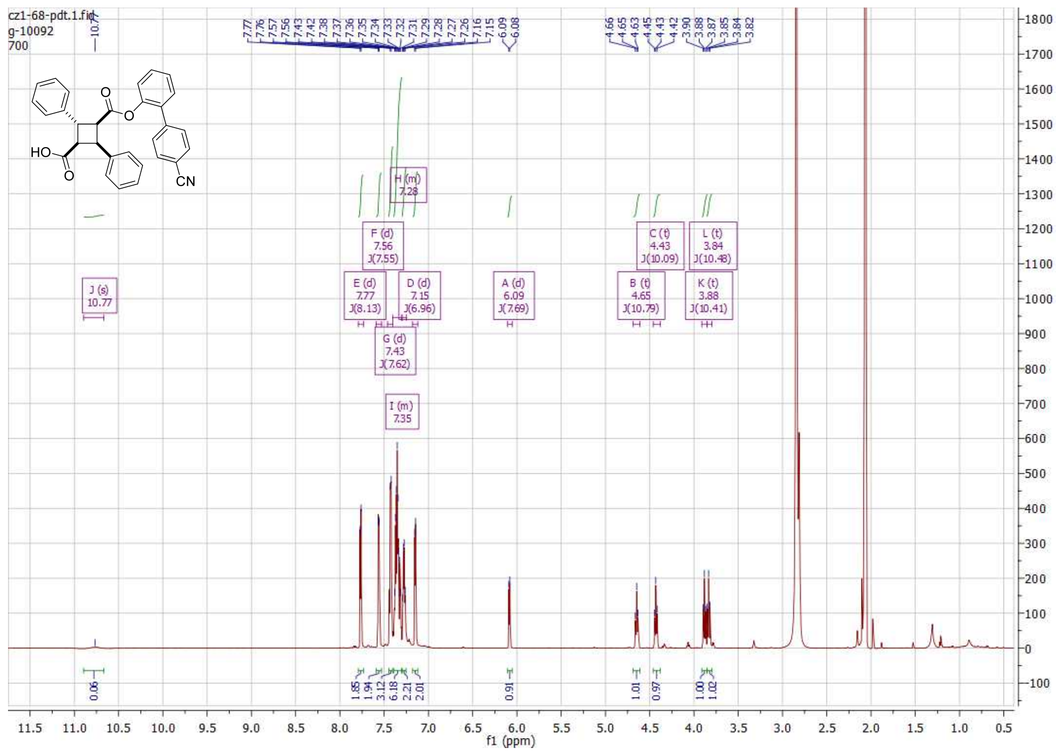
^{1}H NMR of **γ-19**



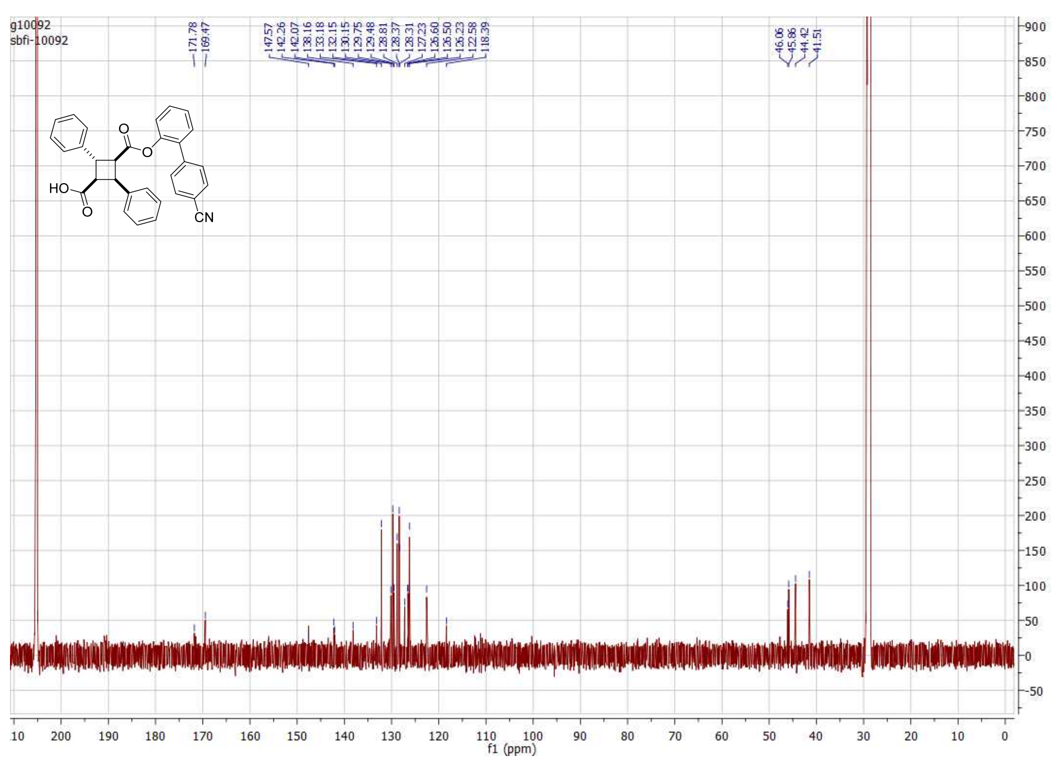
^{13}C NMR of **γ-19**



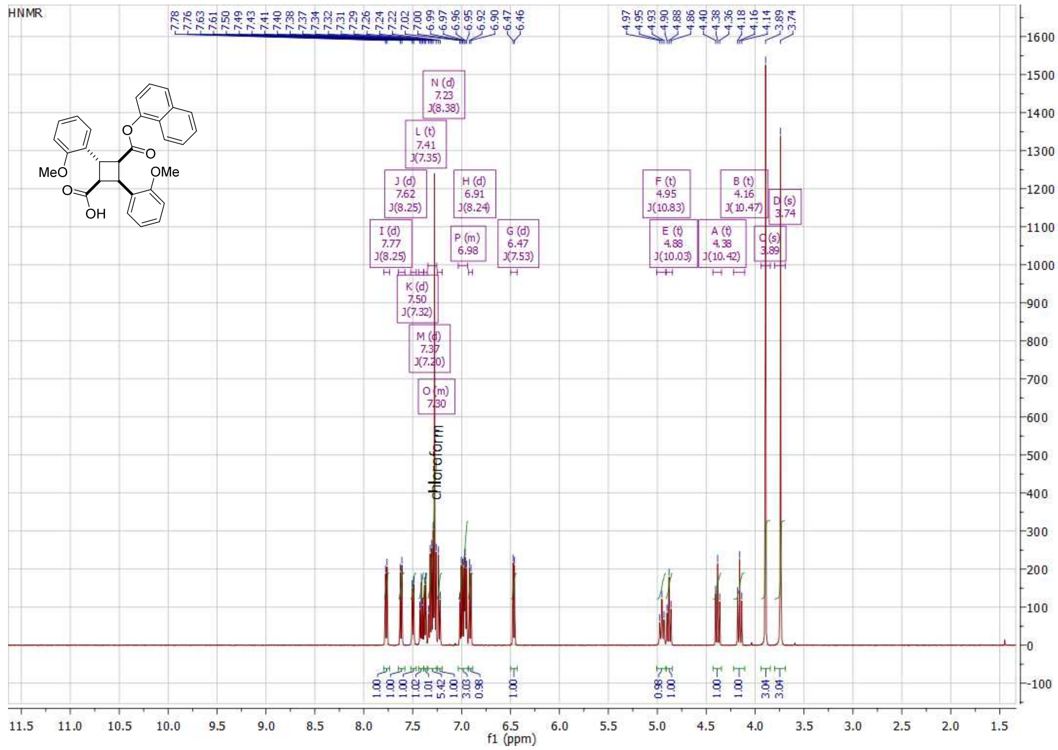
^{1}H NMR of **γ-102**



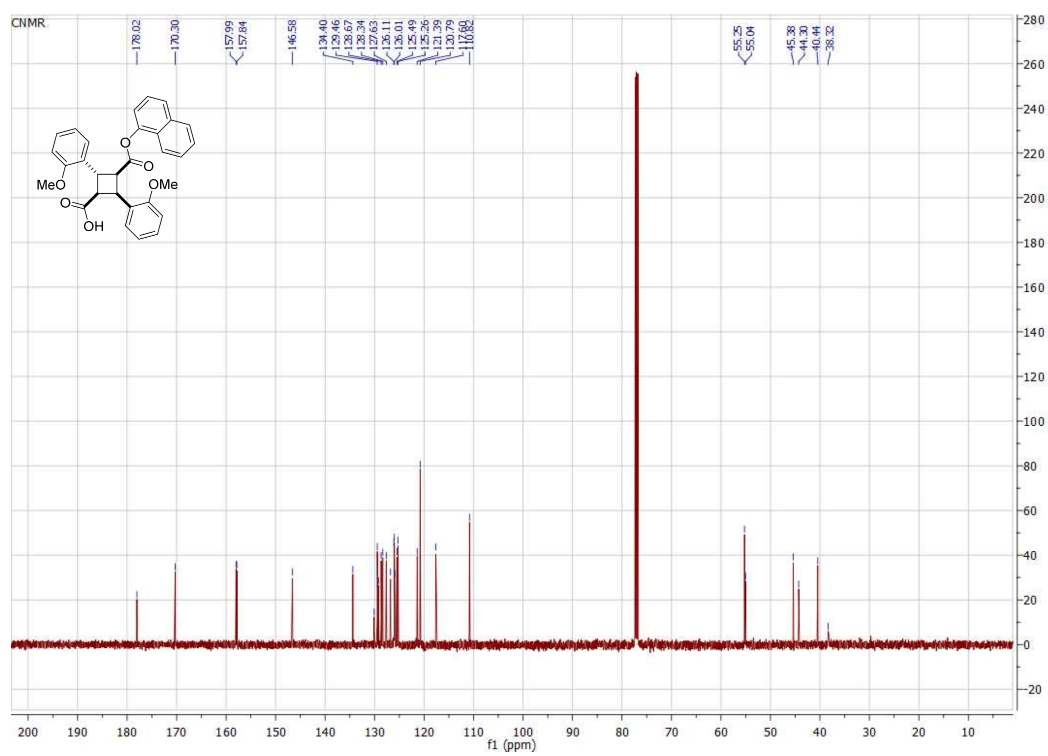
^{13}C NMR of **γ-102**



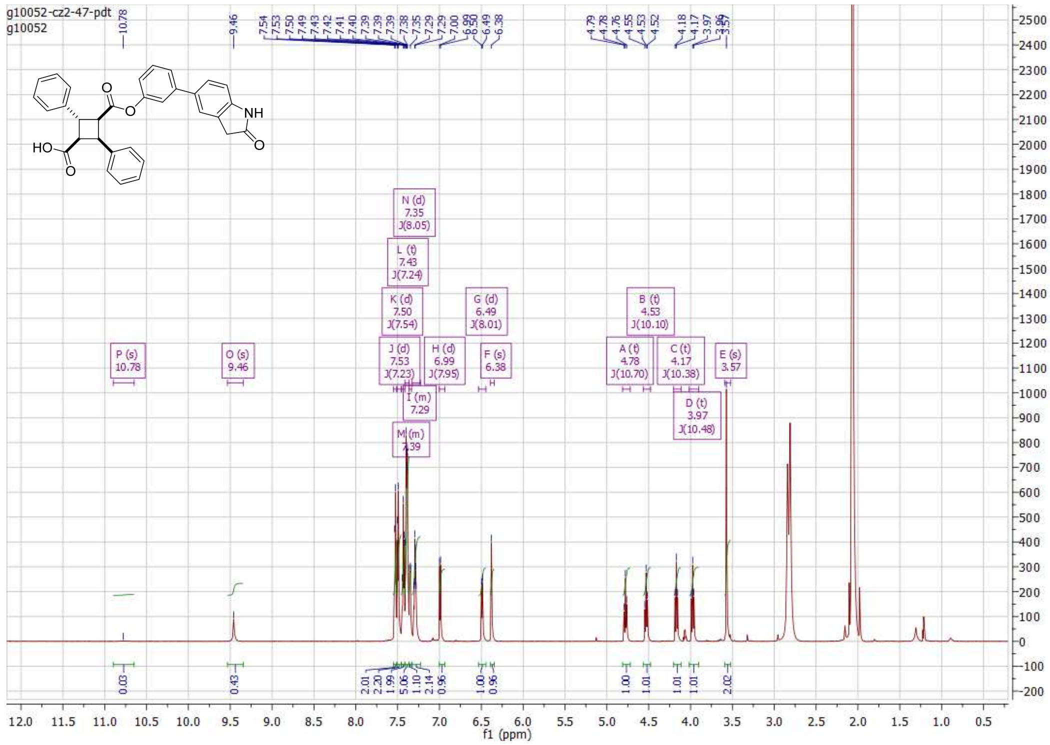
^{1}H NMR of **γ-103**



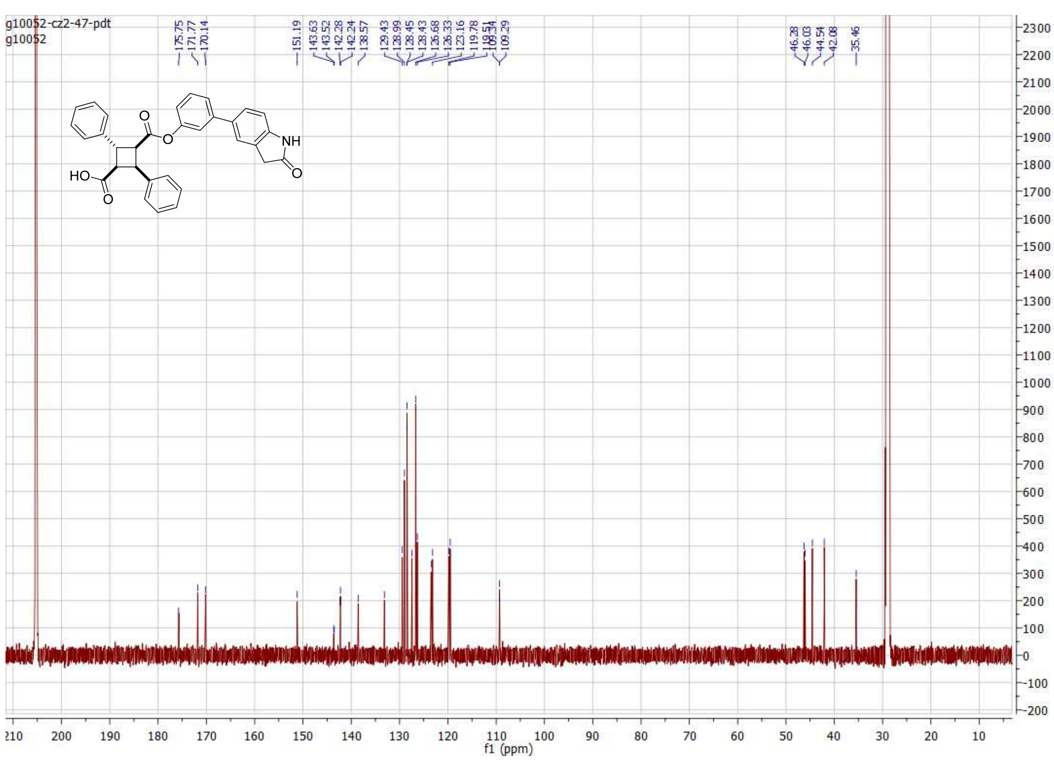
^{13}C NMR of **γ-103**



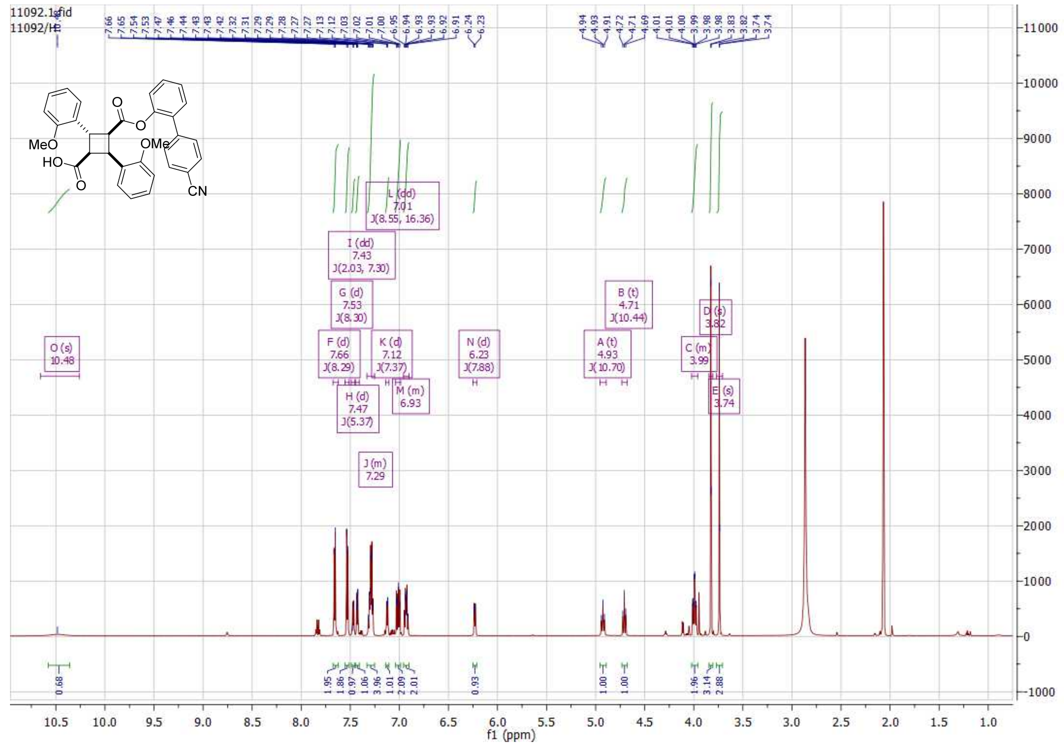
[1]H NMR of **γ-104**



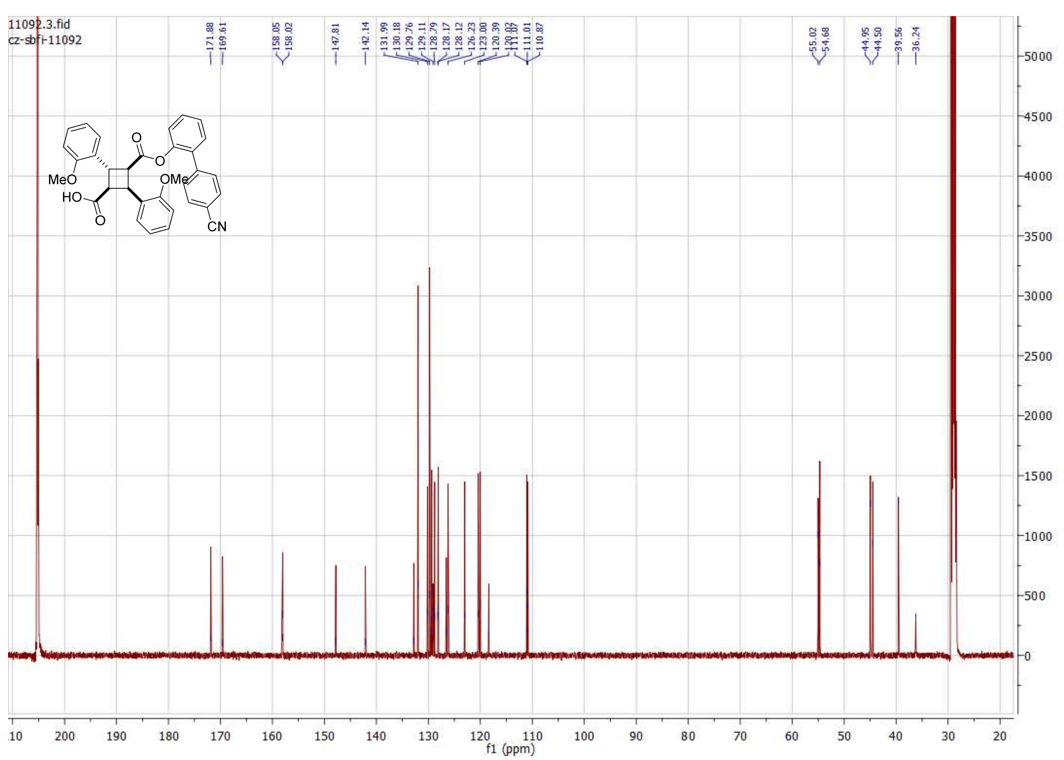
[13]C NMR of **γ-104**



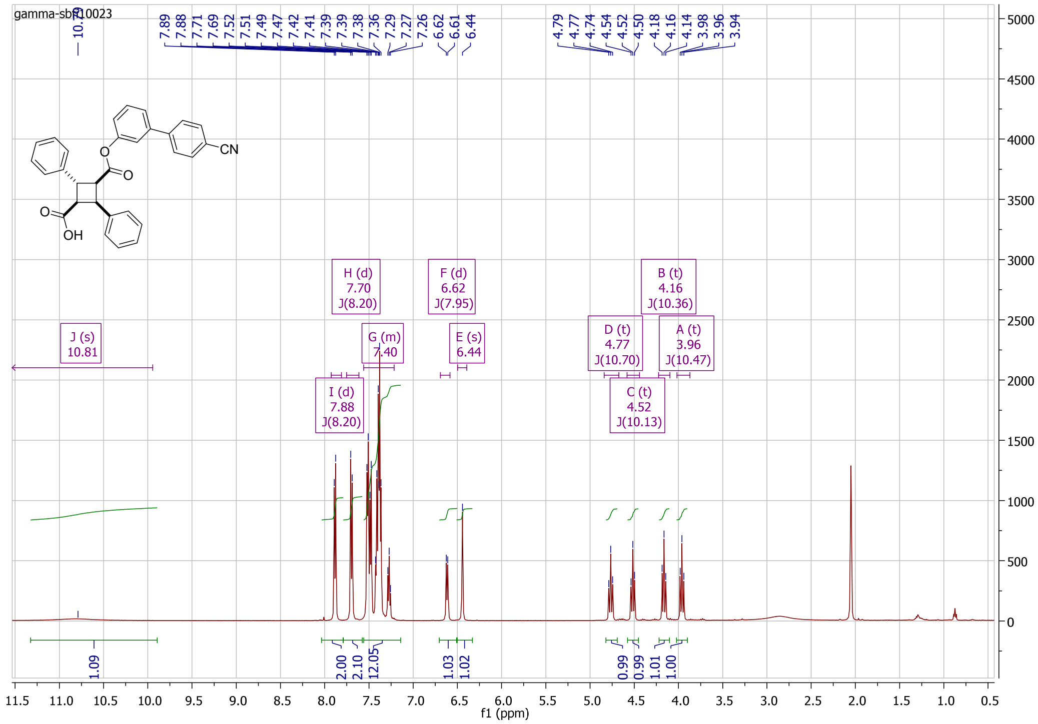
^{1}H NMR of **γ-105**



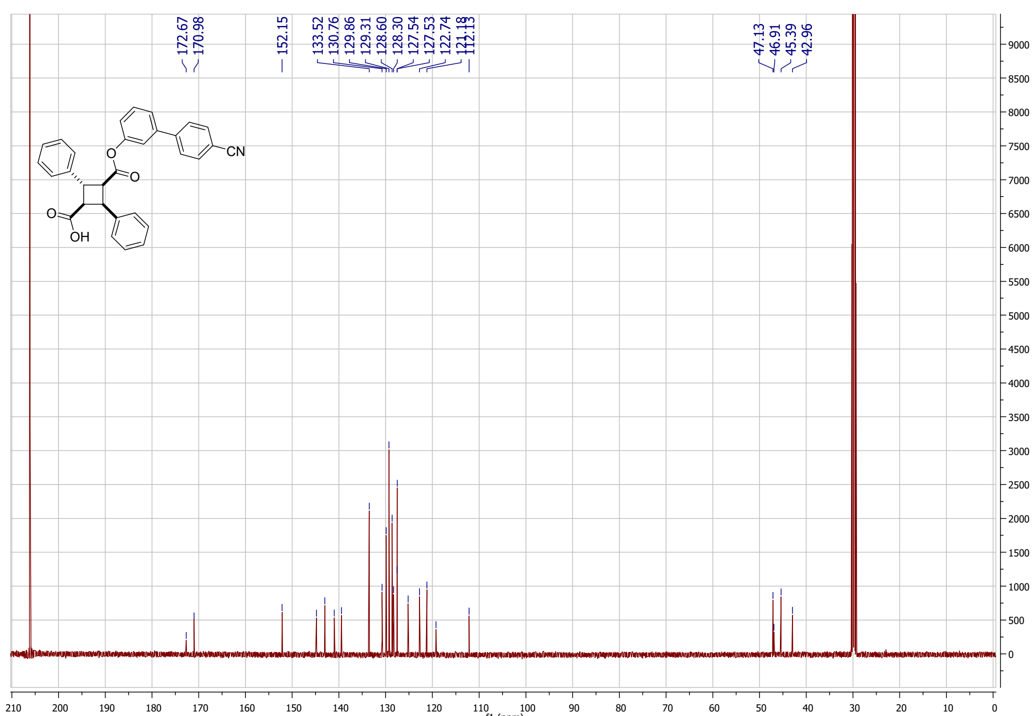
^{13}C NMR of **γ-105**



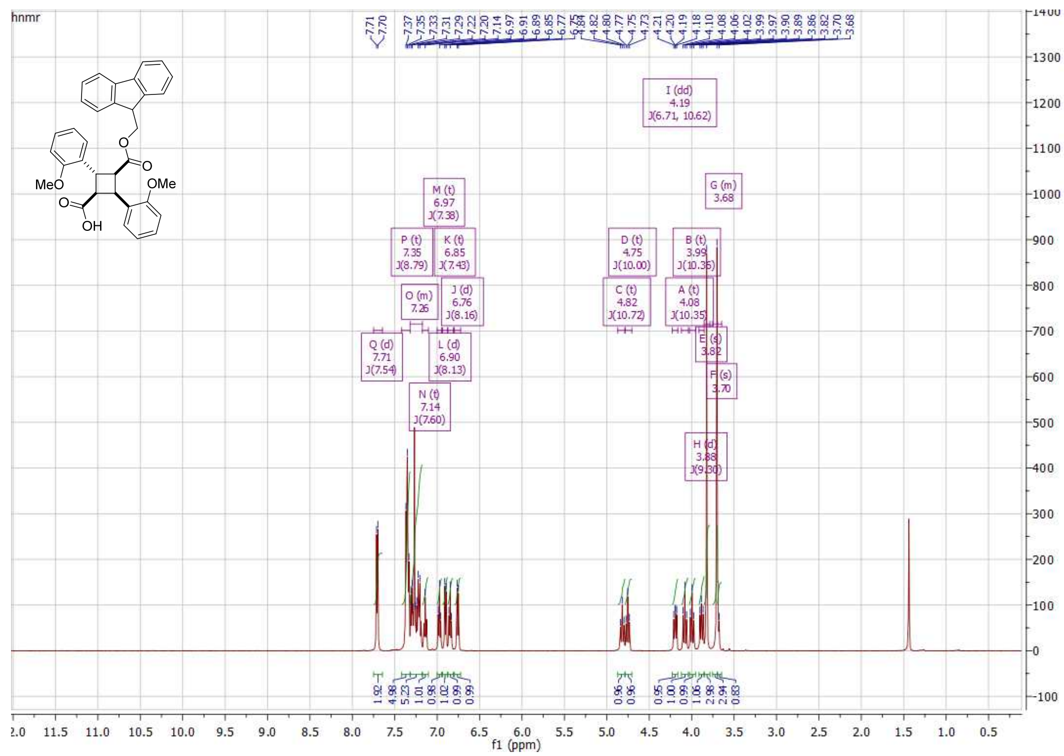
^{1}H NMR of **γ-106**



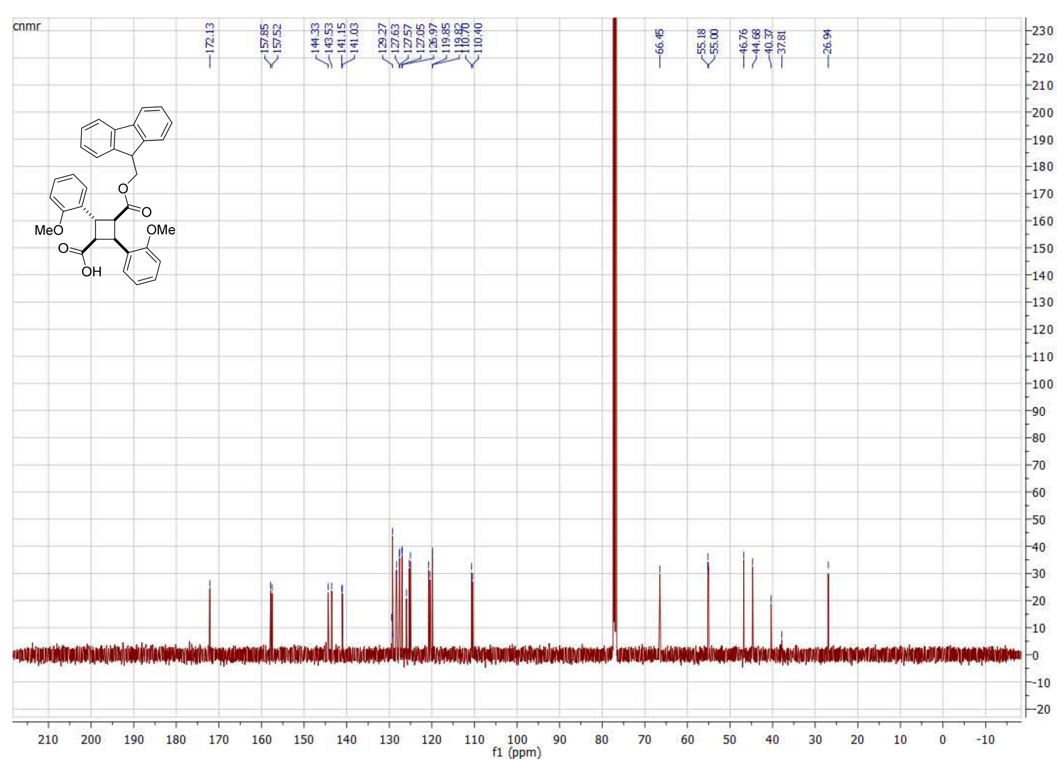
^{13}C NMR of **γ-106**



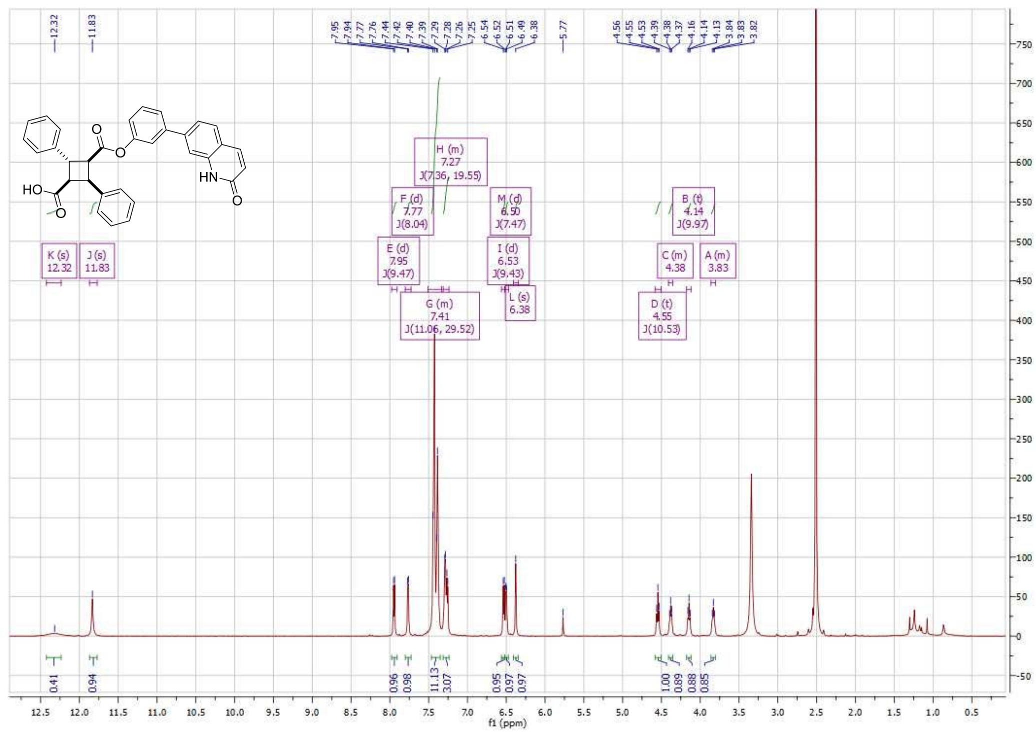
^{1}H NMR of **γ-107**



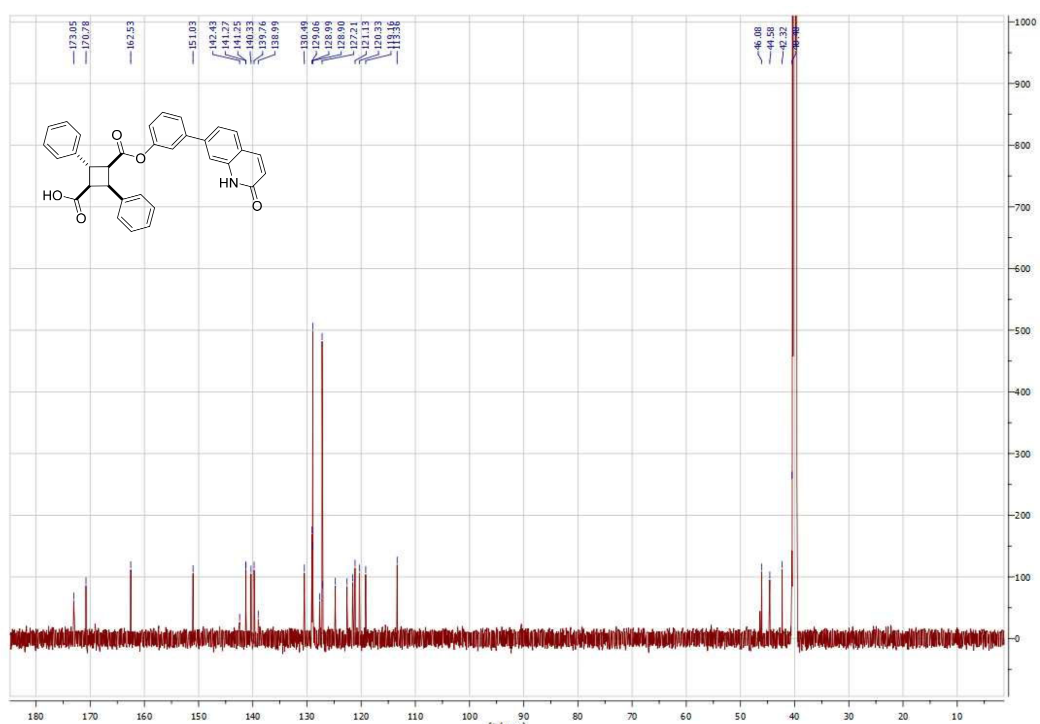
^{13}C NMR of **γ-107**



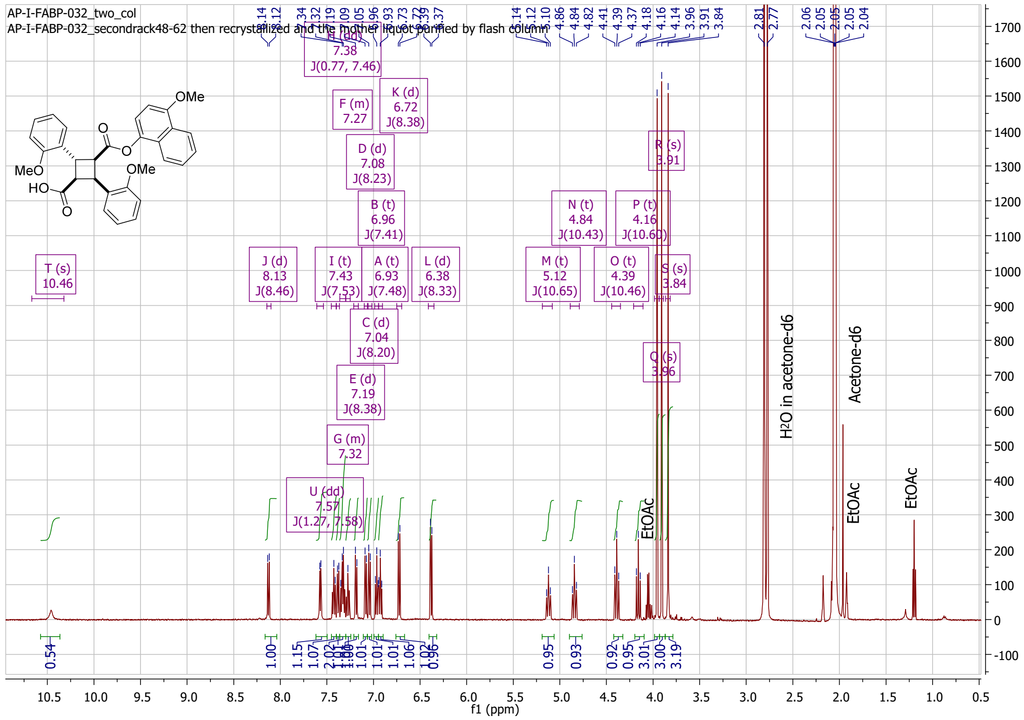
^{1}H NMR of **γ-108**



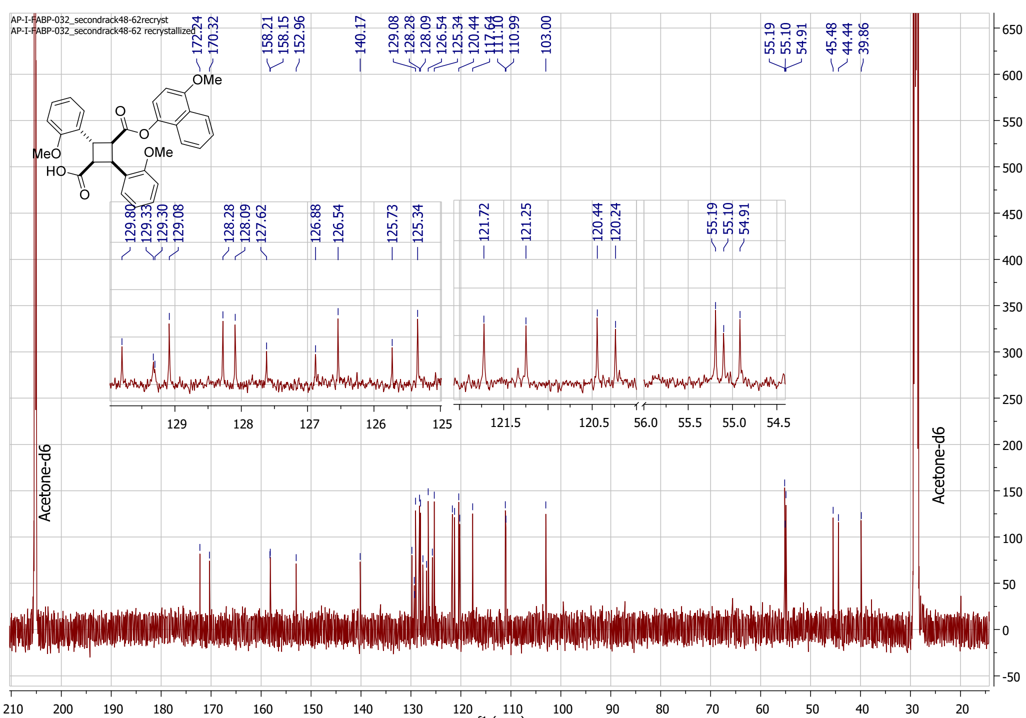
^{13}C NMR of **γ-108**



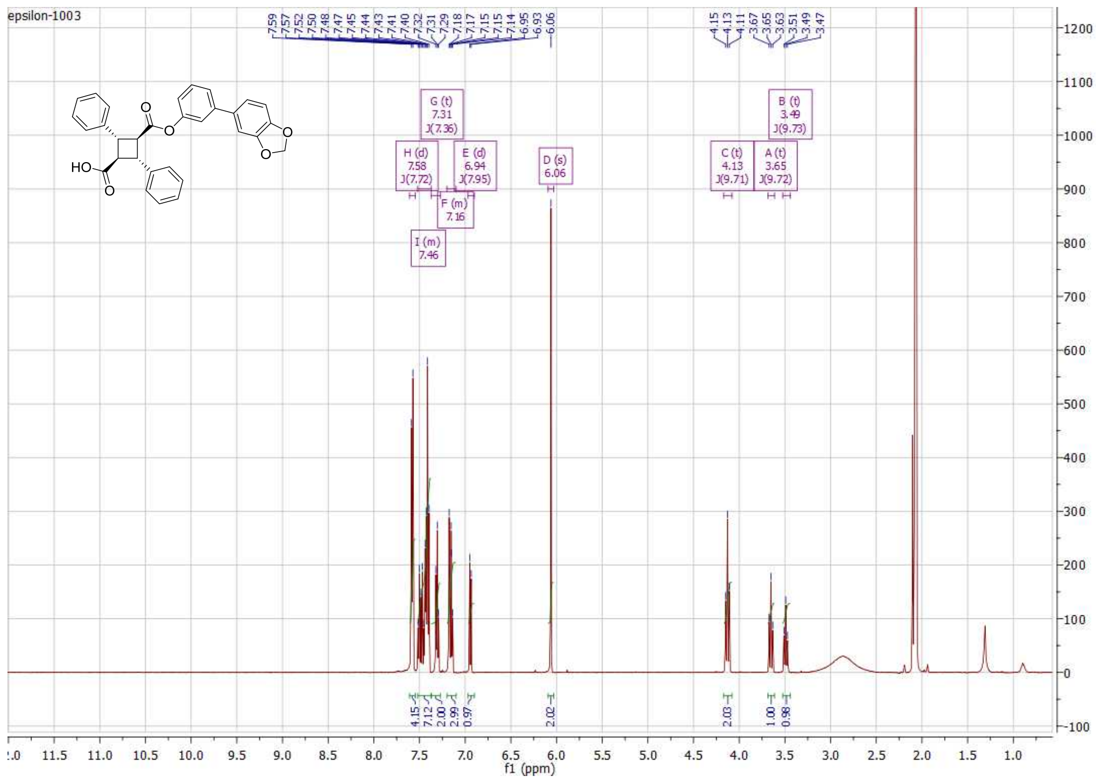
[1]H NMR of **γ-109**



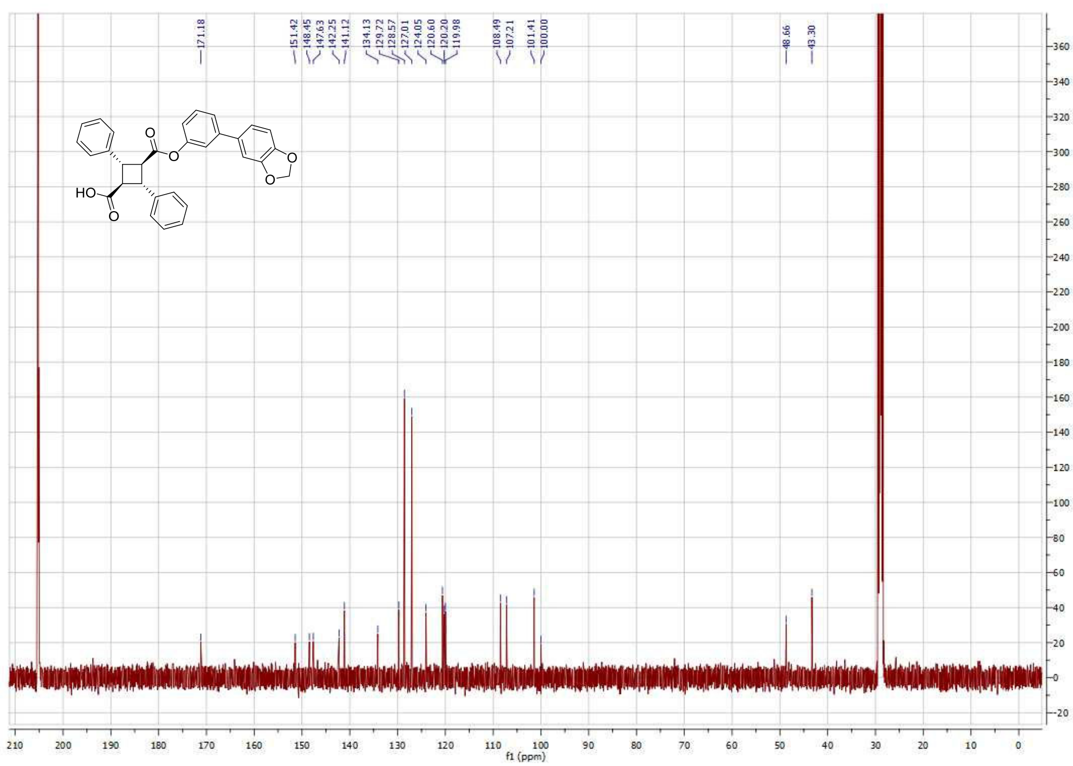
[13]C NMR of **γ-109**



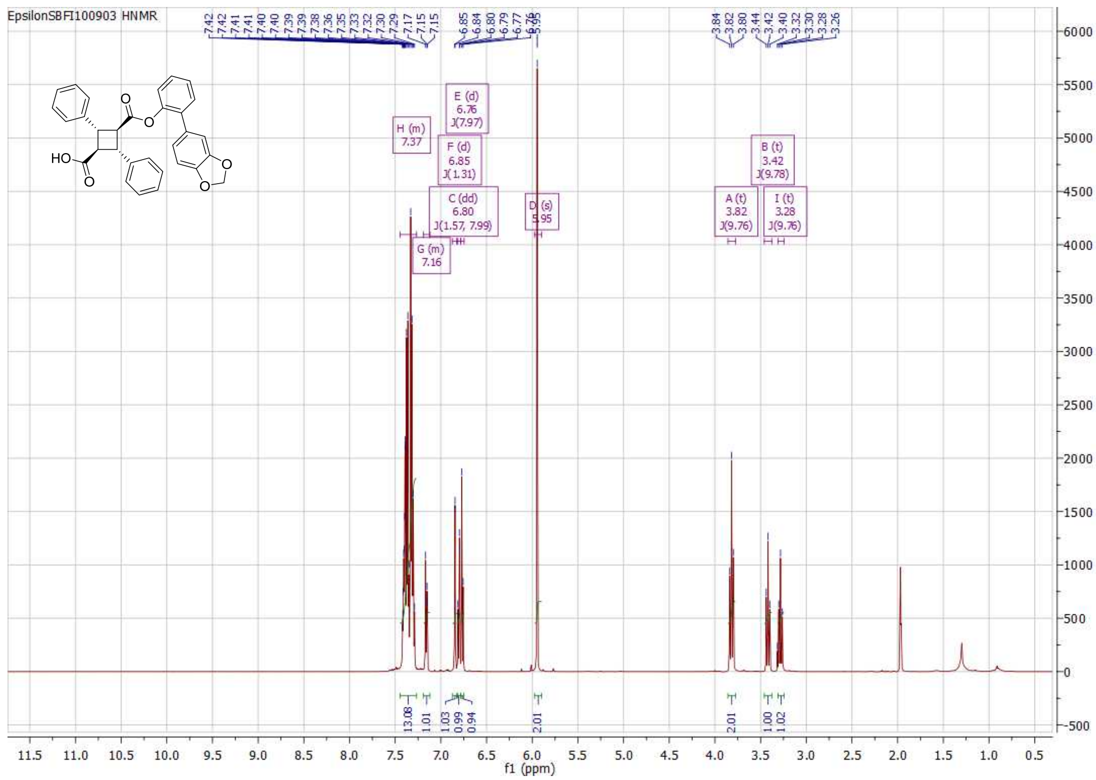
[1]H NMR of **ε-5**



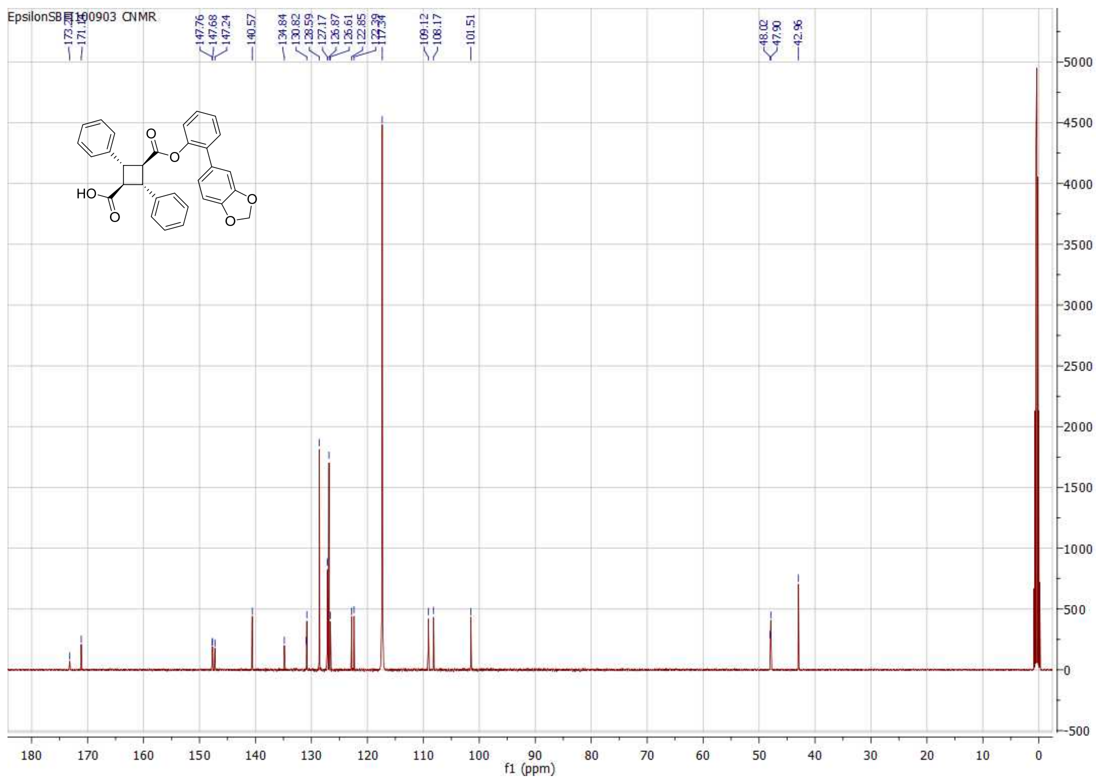
[13]C NMR of **ε-5**



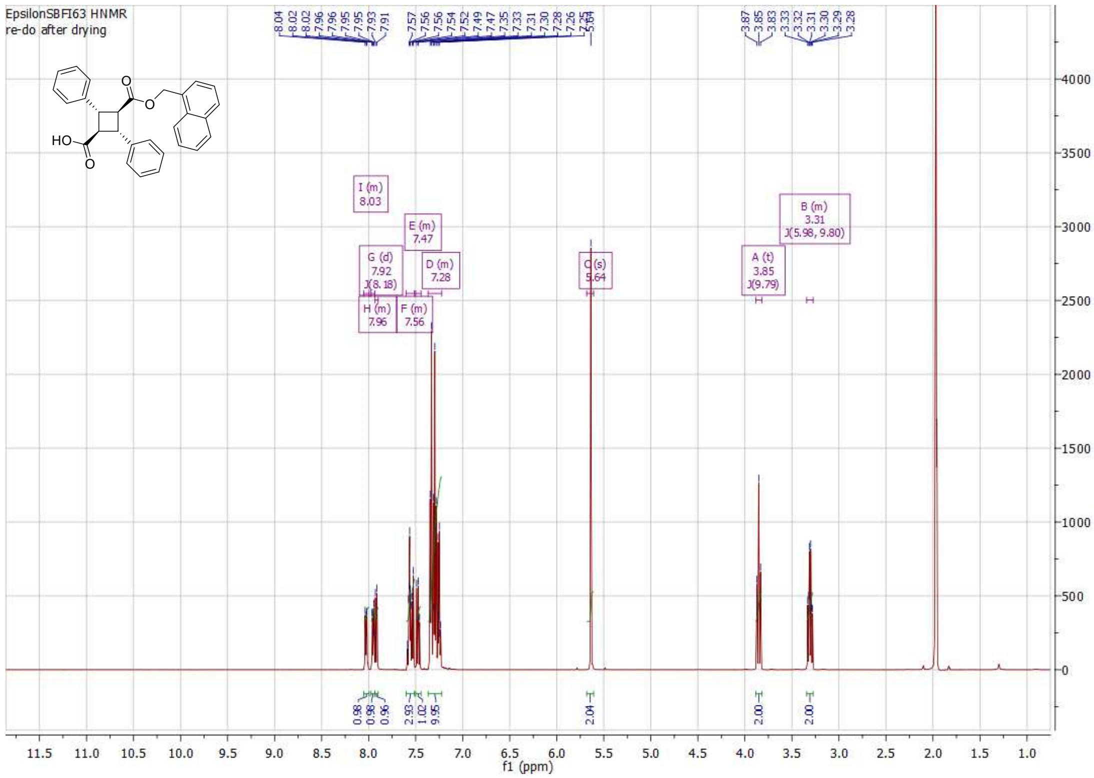
^{1}H NMR of **ε-11**



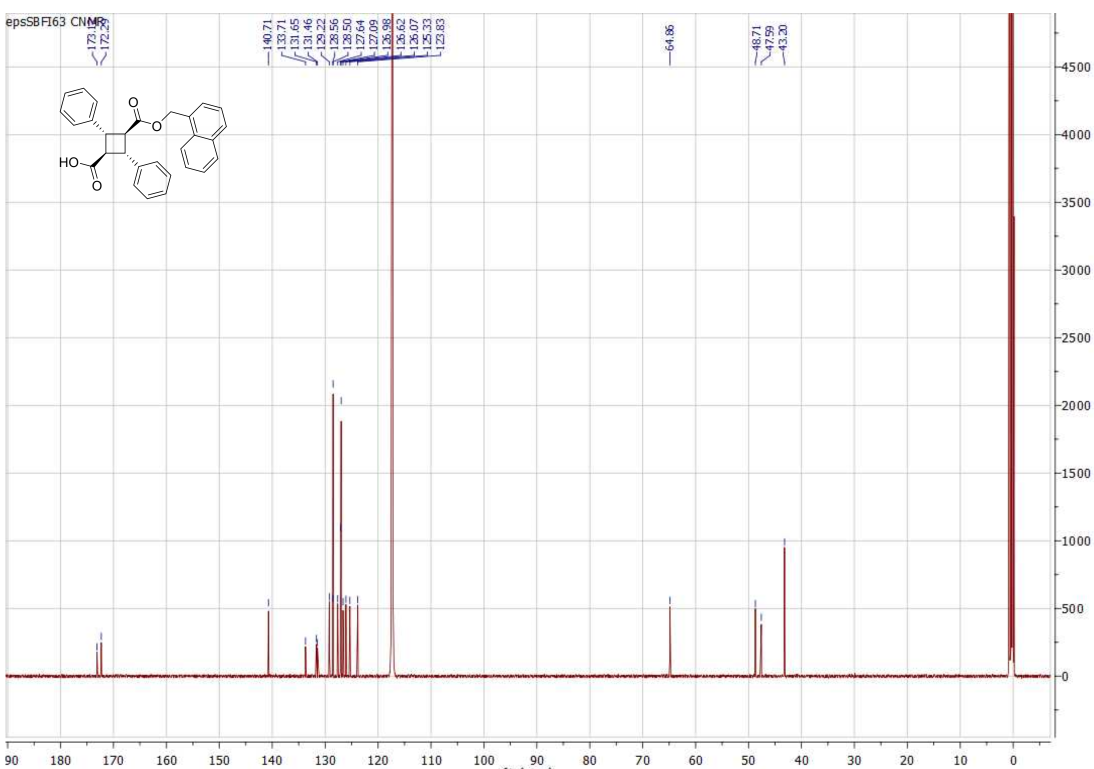
^{13}C NMR of **ε-11**



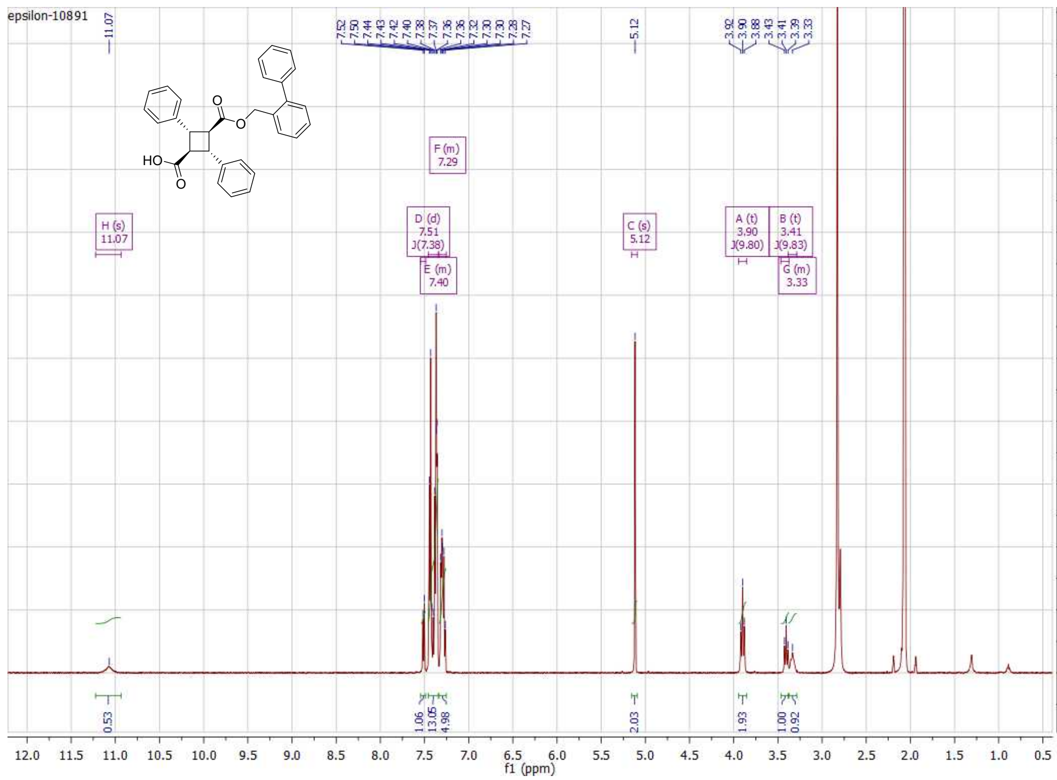
[1]H NMR of **ε-23**



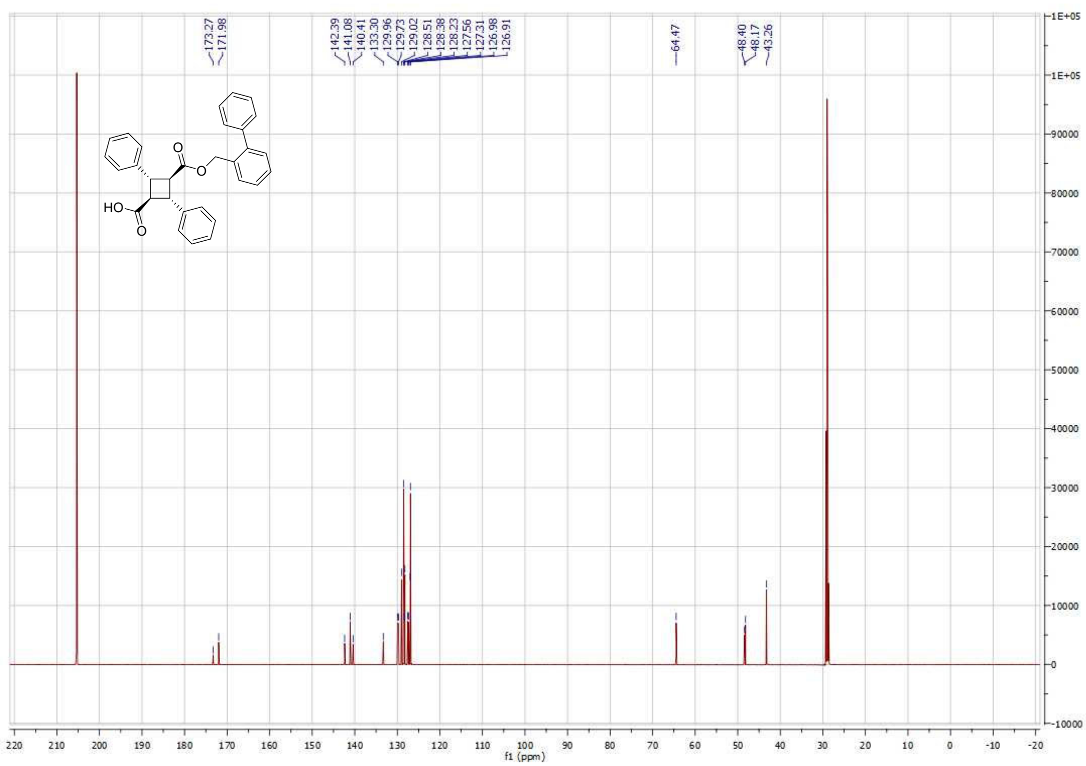
[13]C NMR of **ε-23**



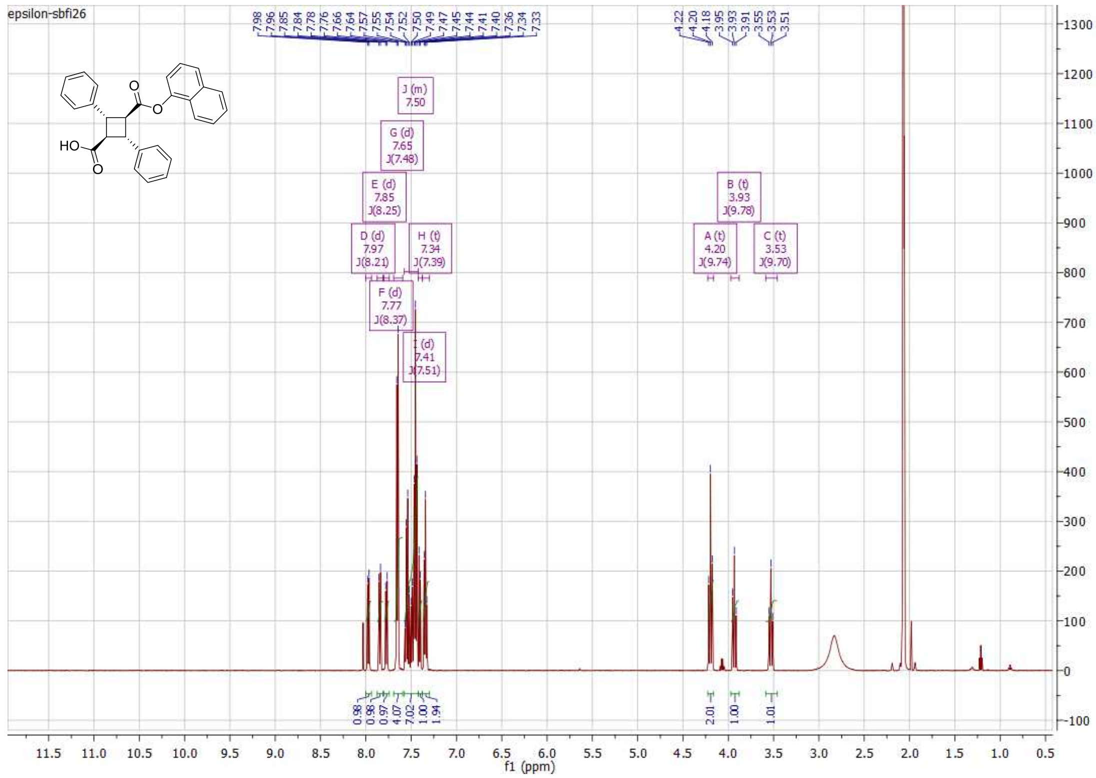
^{1}H NMR of **ε-201**



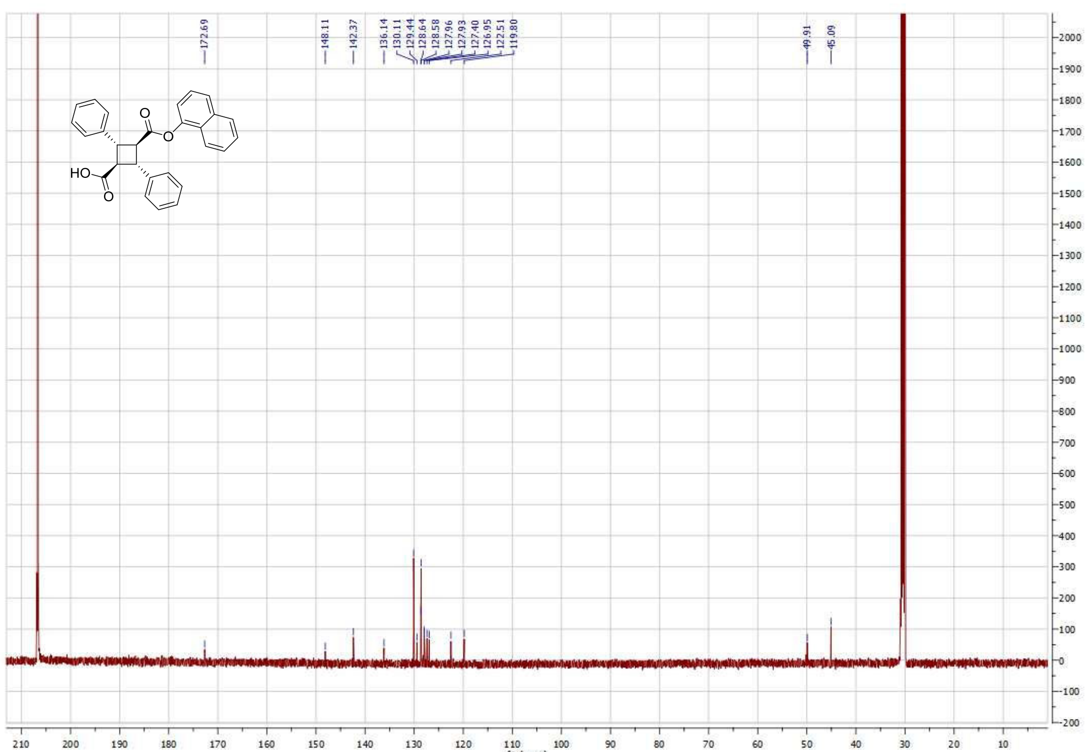
^{13}C NMR of **ε-201**



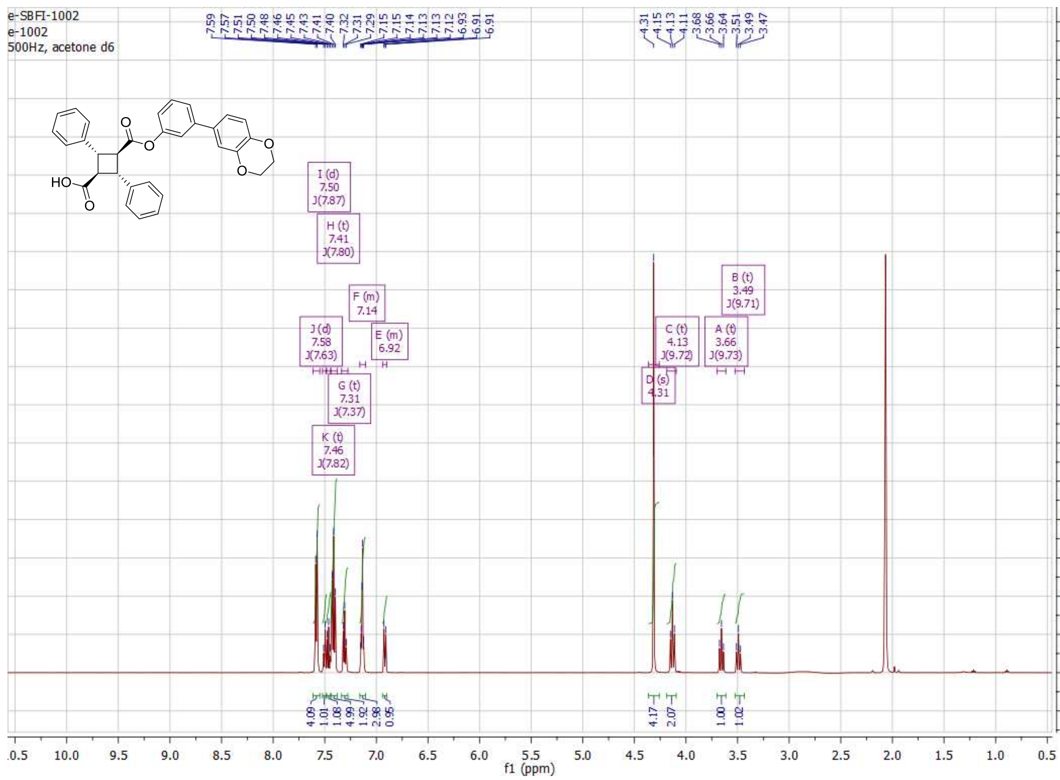
^{1}H NMR of **ε-202**



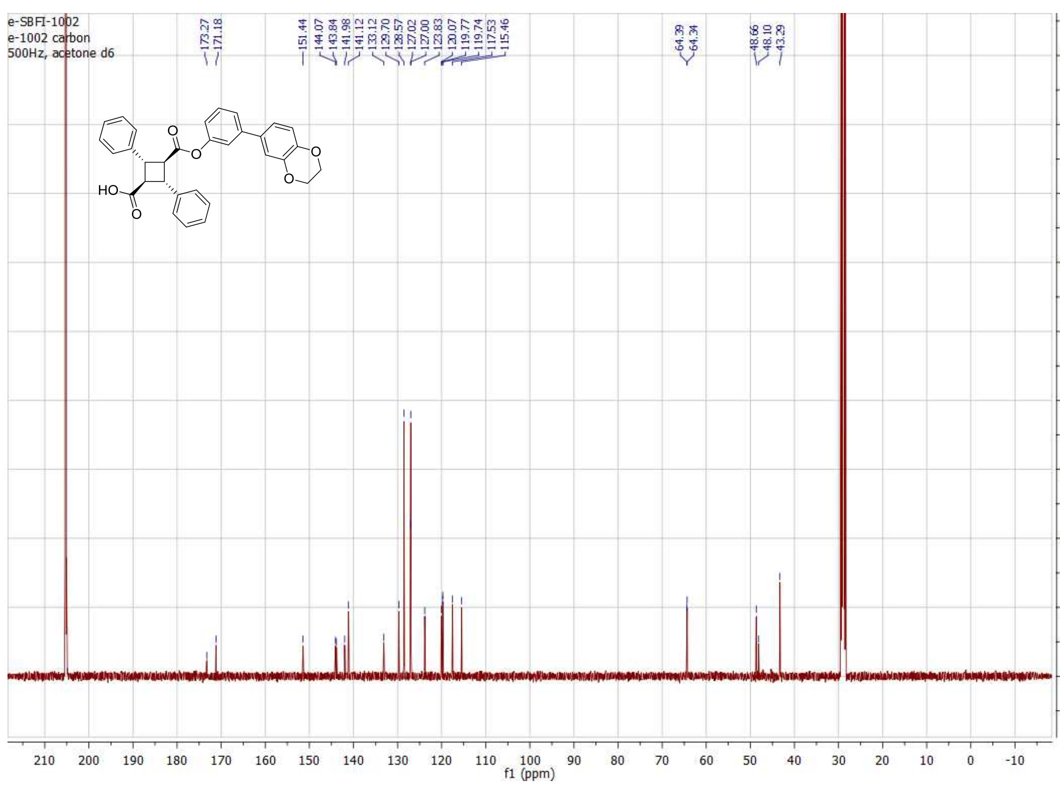
^{13}C NMR of **ε-202**



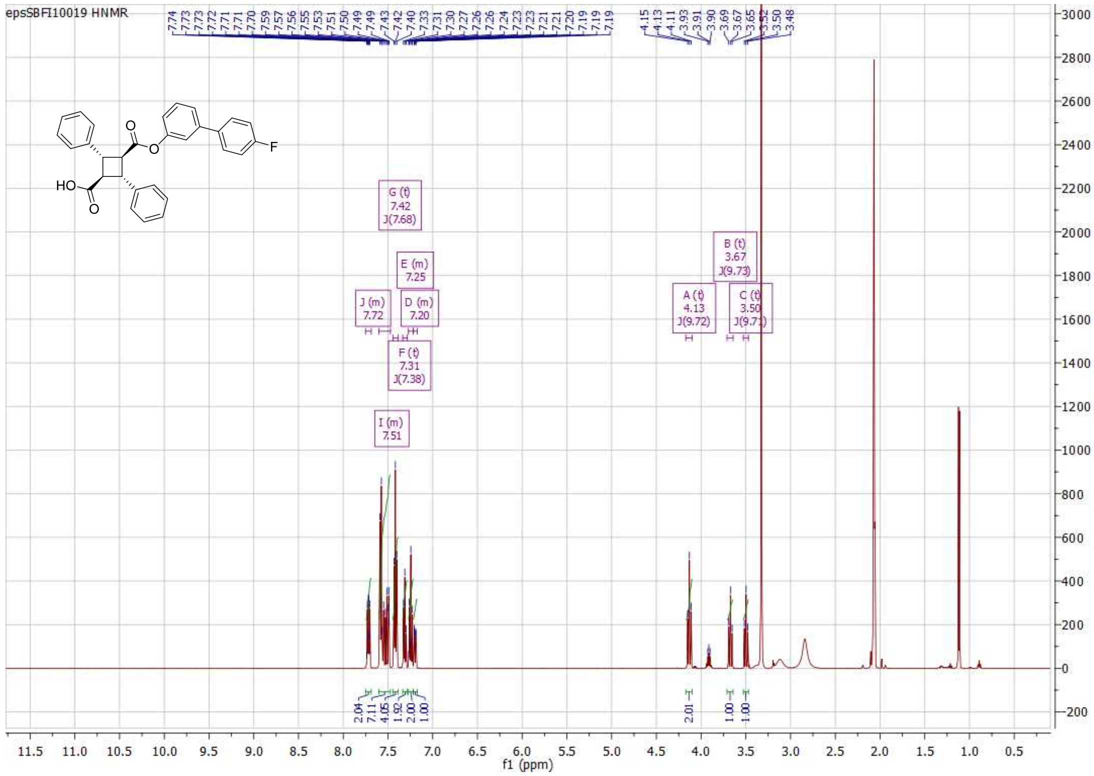
[1]H NMR of **ε-203**



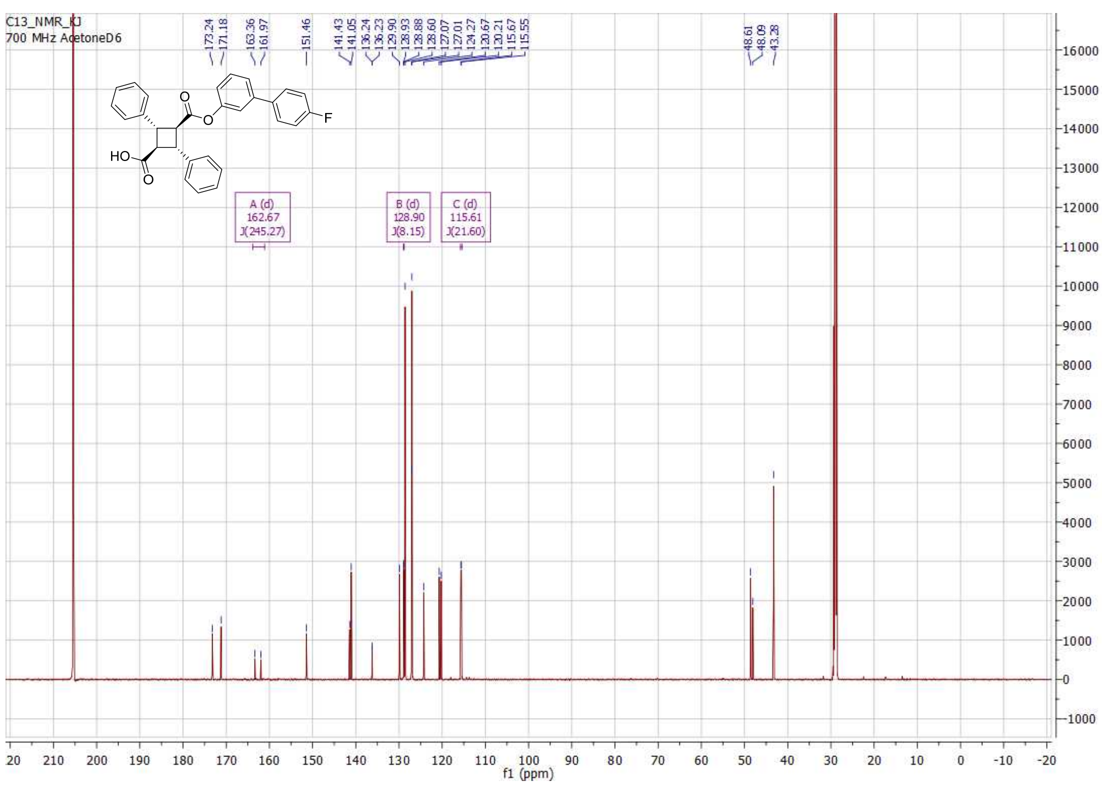
[13]C NMR of **ε-203**



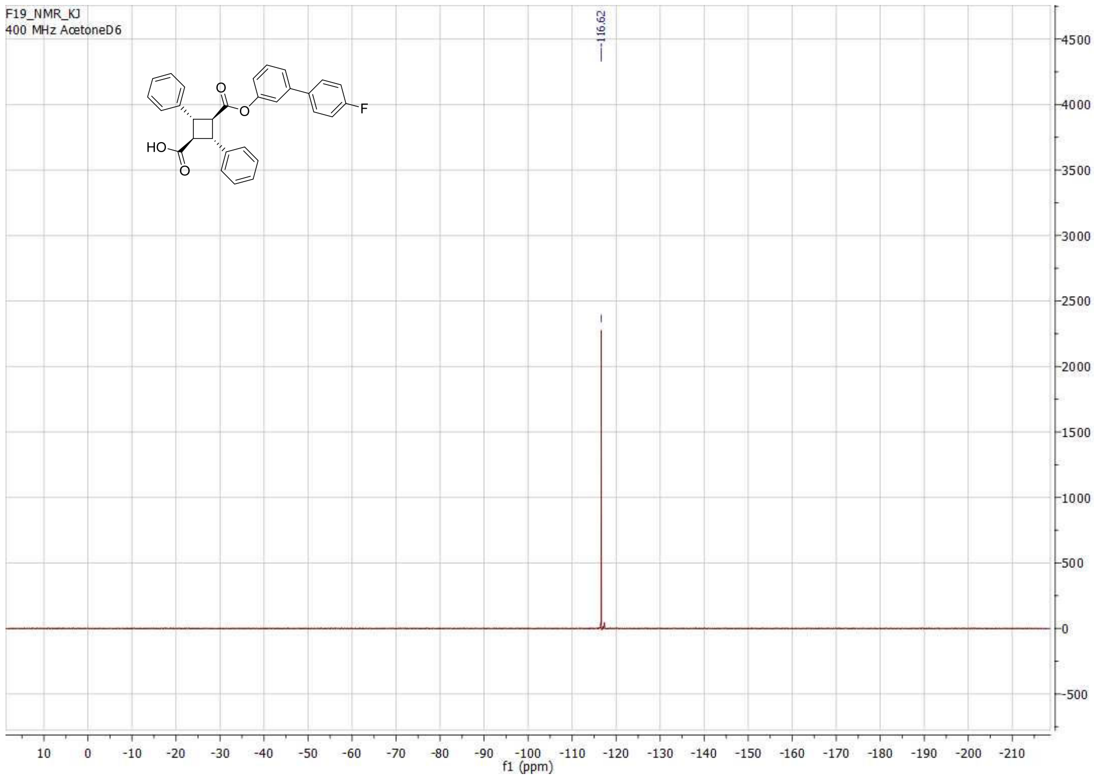
^{1}H NMR of **ε-204**



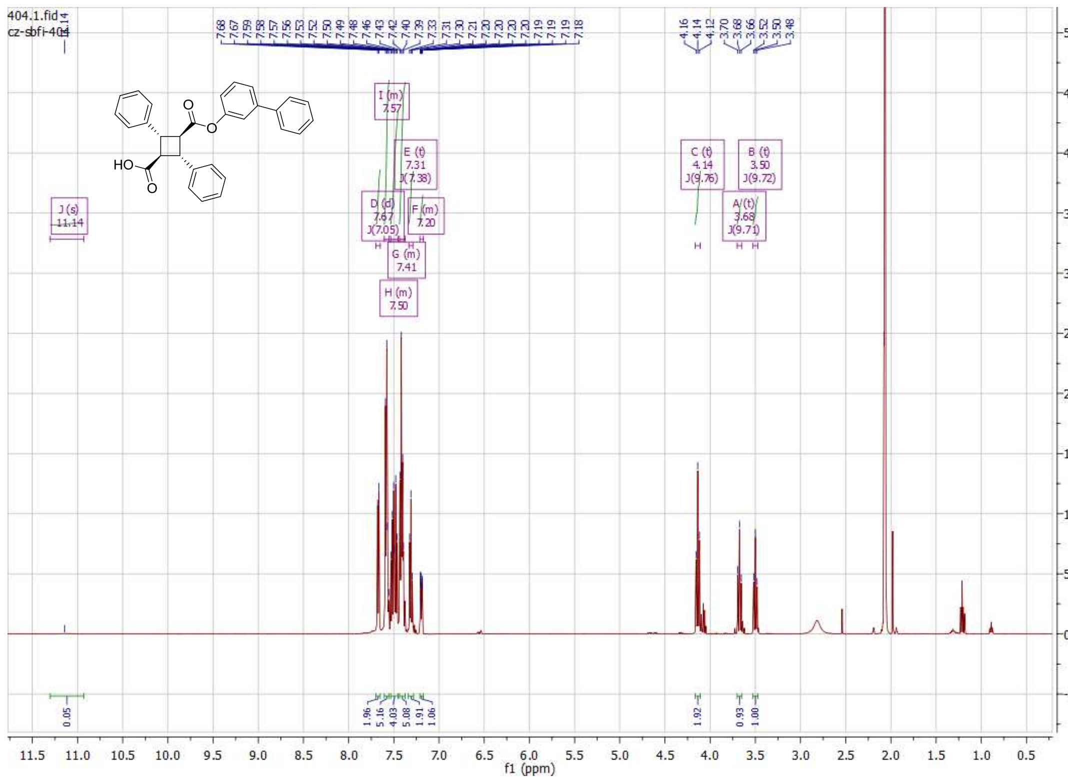
^{13}C NMR of **ε-204**



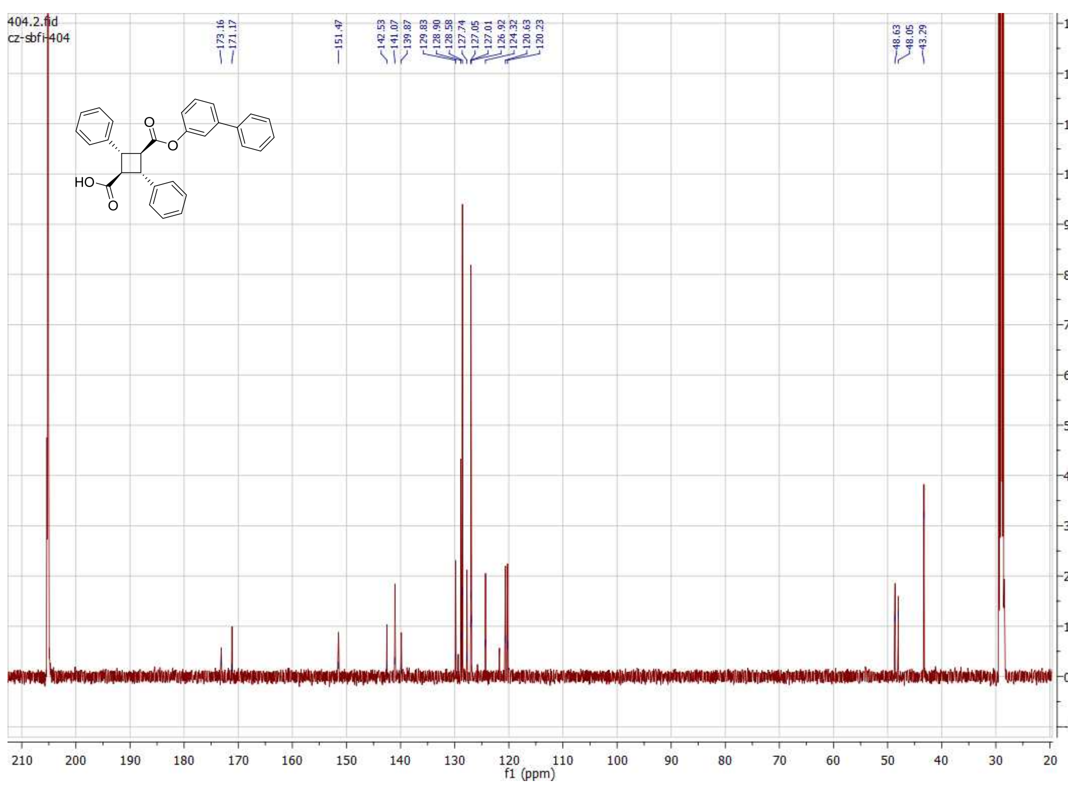
^{19}F NMR of **ε-204**



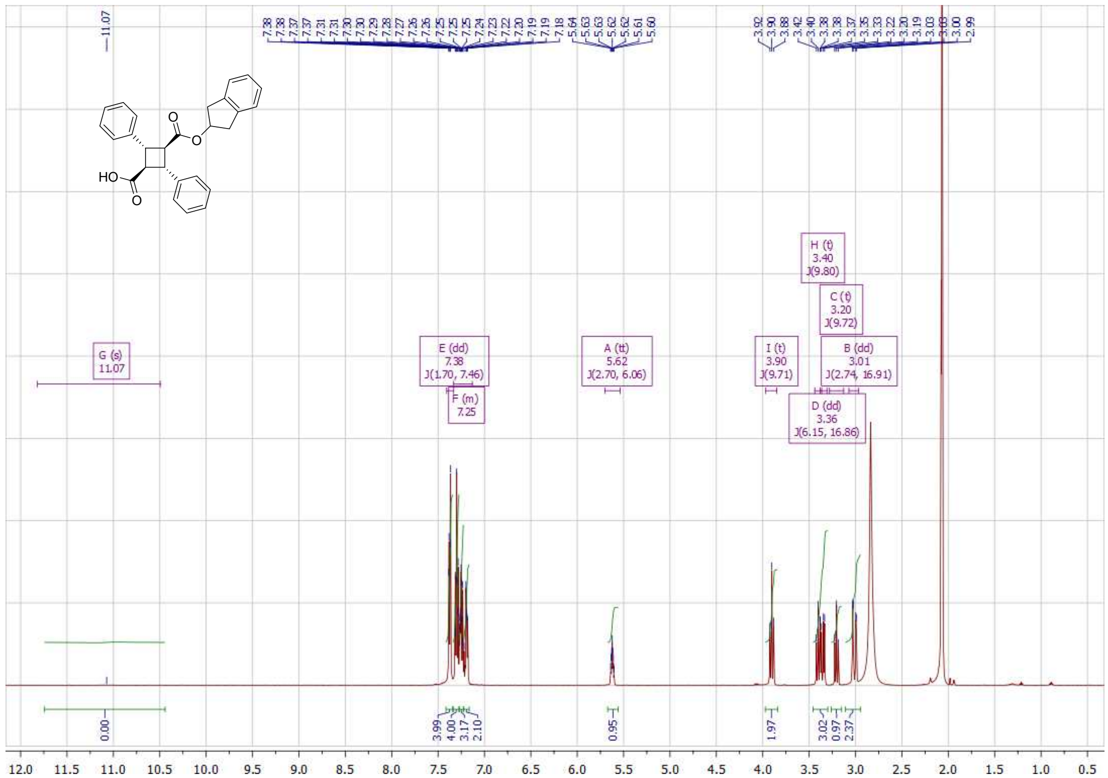
[1]H NMR of **ε-206**



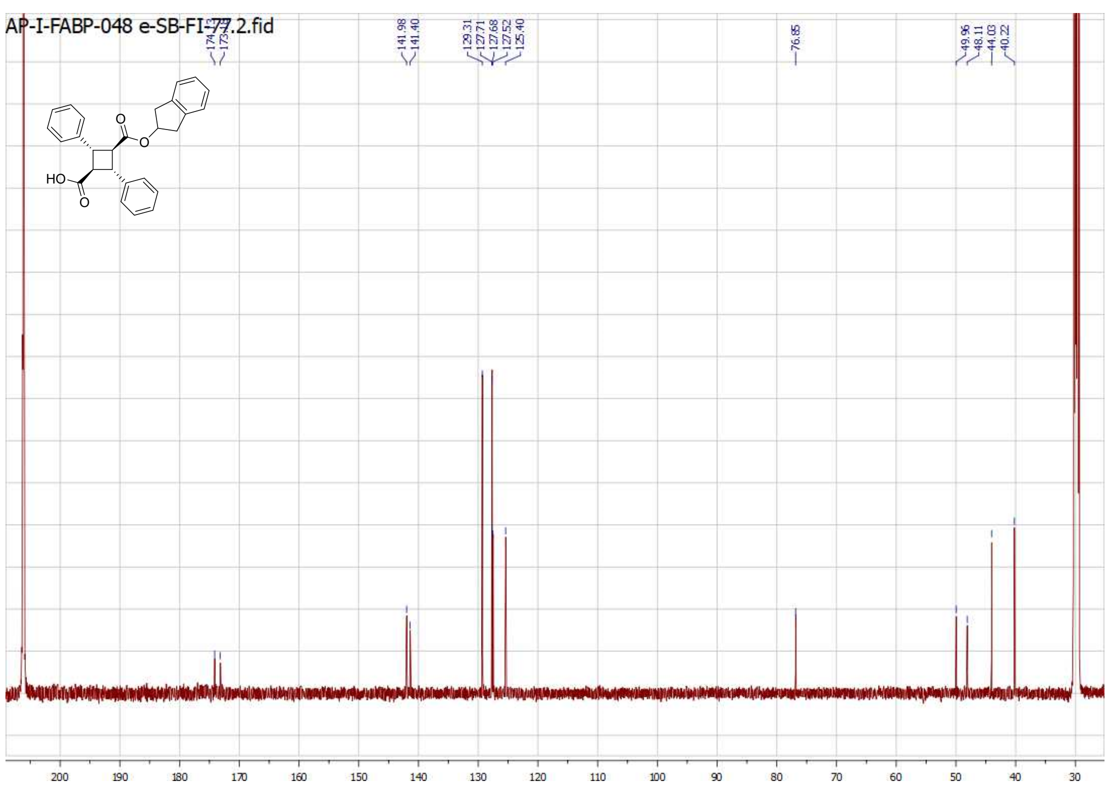
[13]C NMR of **ε-206**



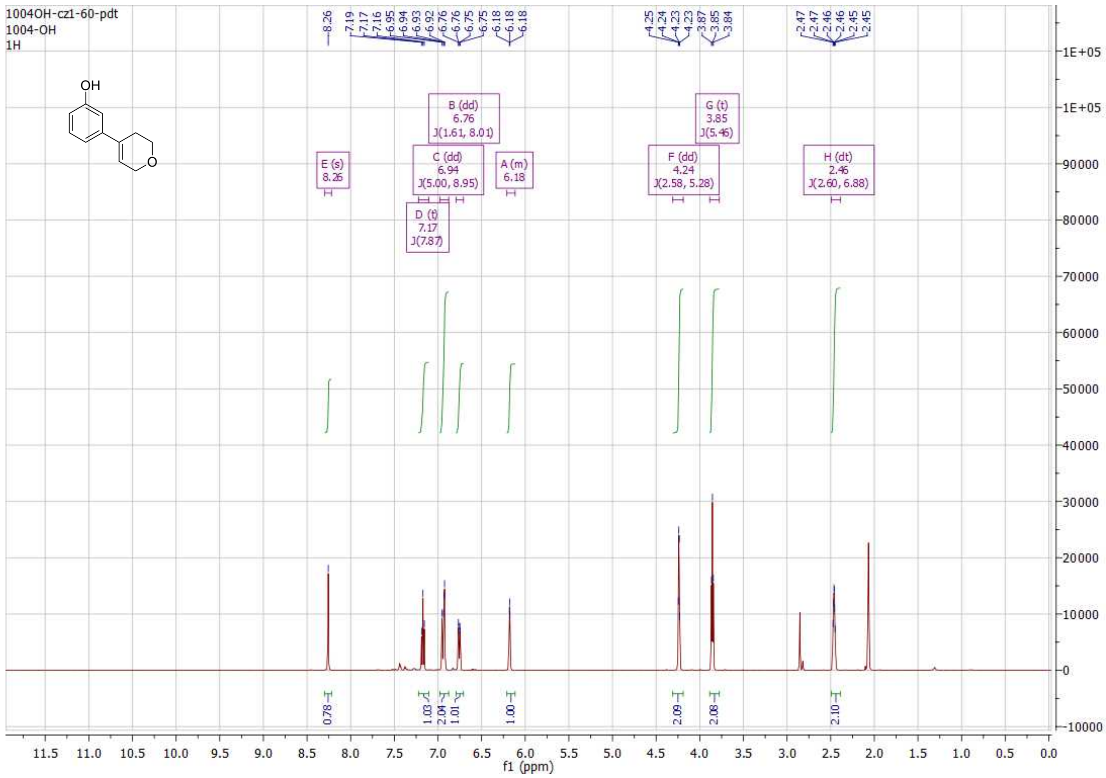
[1]H NMR of **ε-207**



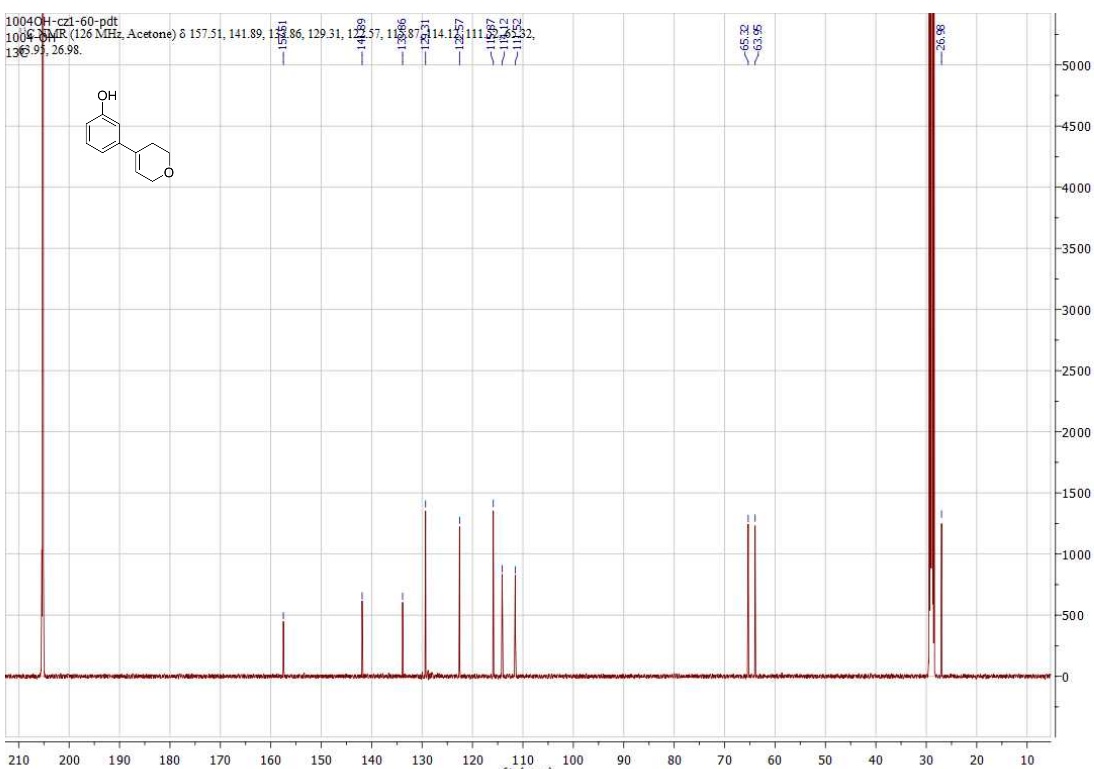
[13]C NMR of **ε-207**



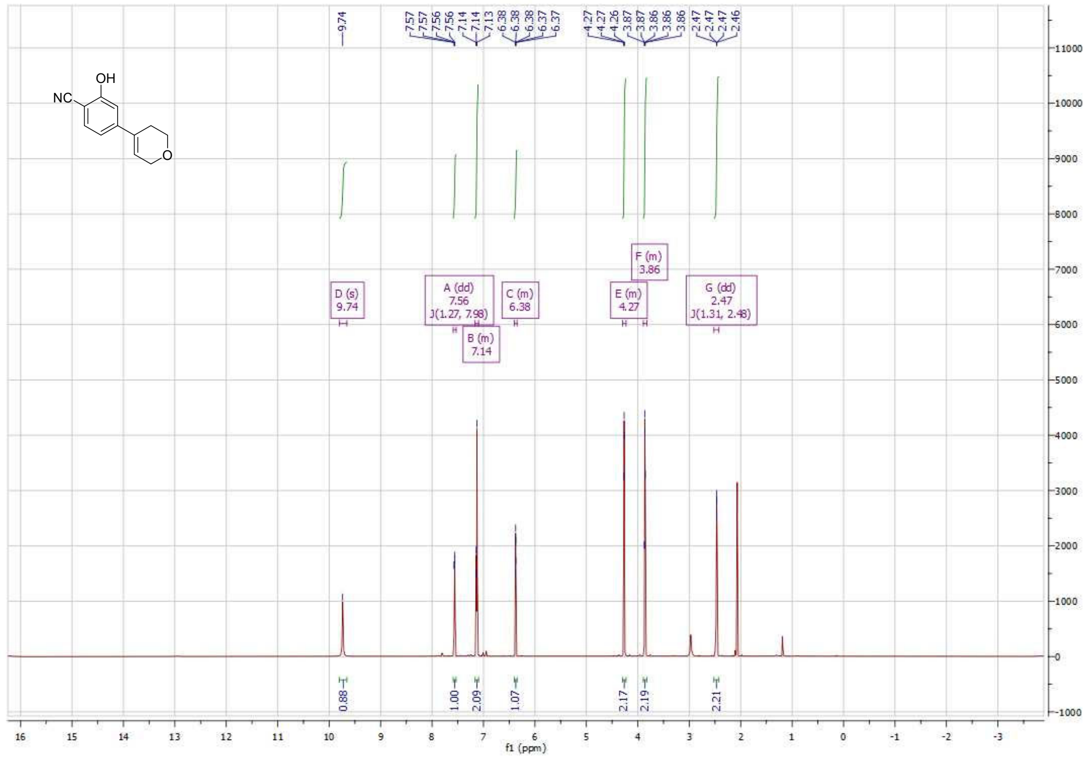
^{1}H NMR of (**A-1**)



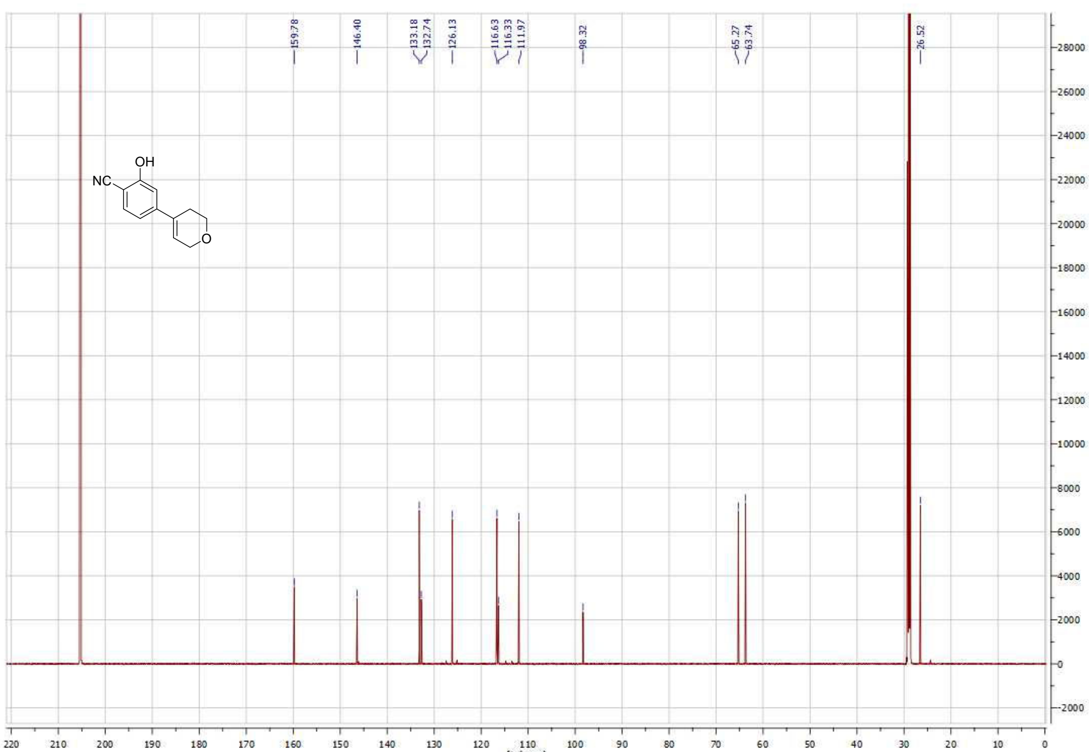
^{13}C NMR of (**A-1**)



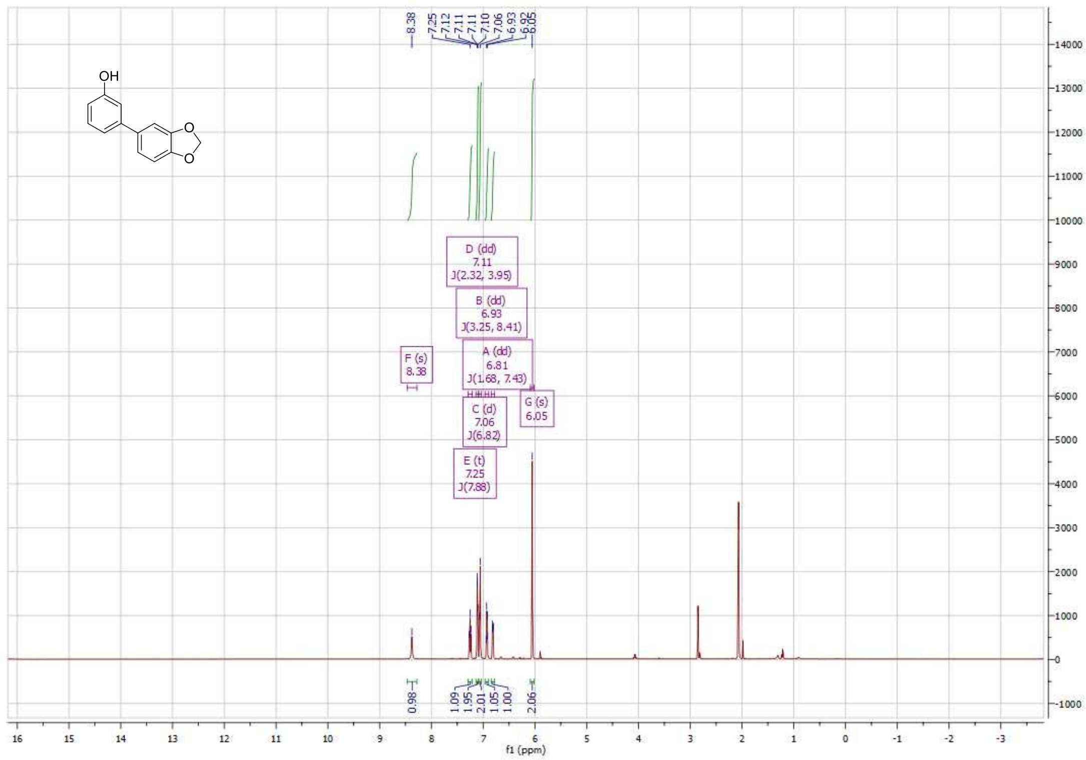
^{1}H NMR of (**A-2**)



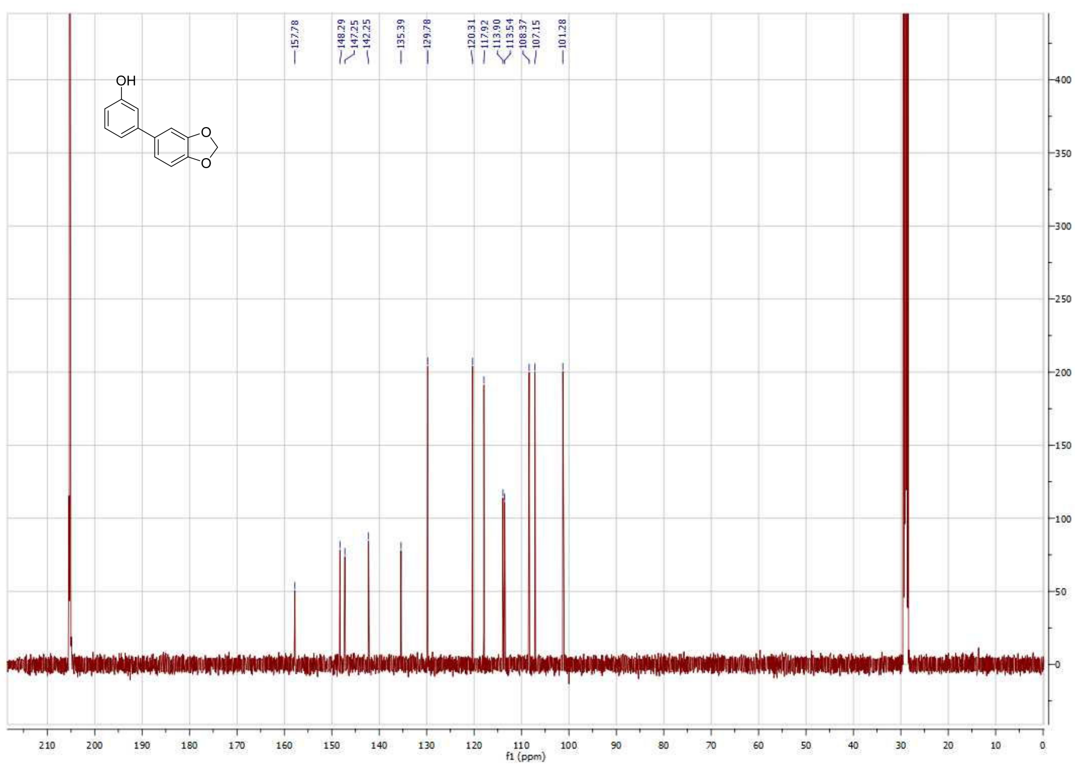
^{13}C NMR of (**A-2**)



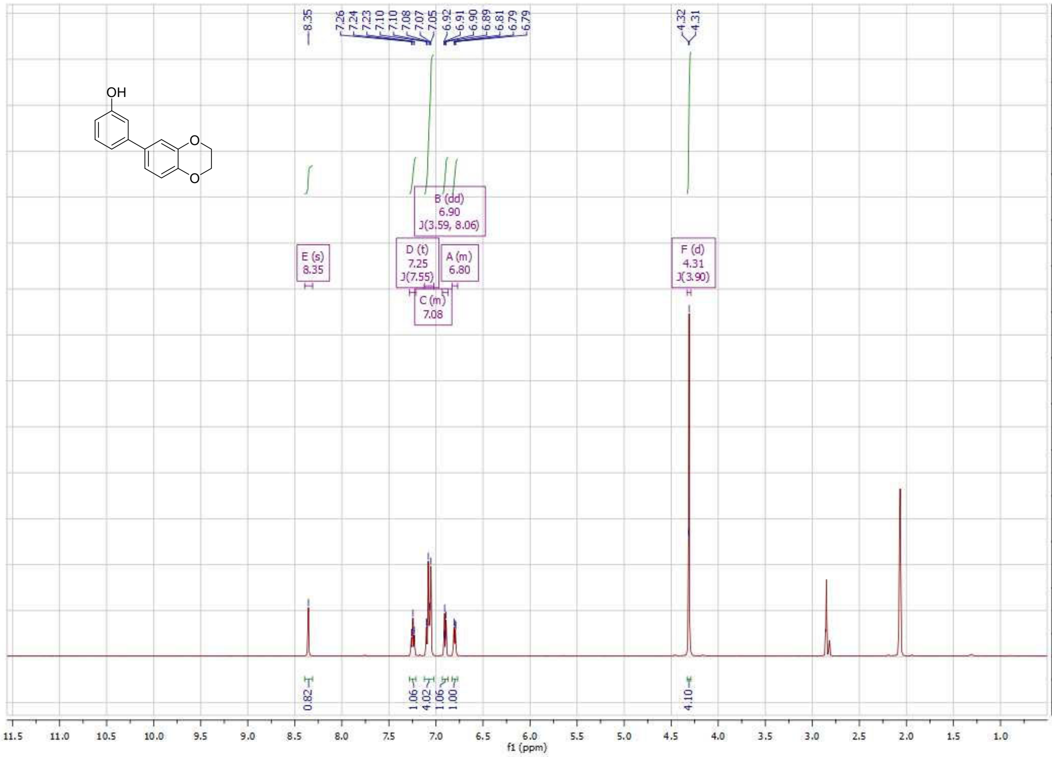
^{1}H NMR of (**A-3**)



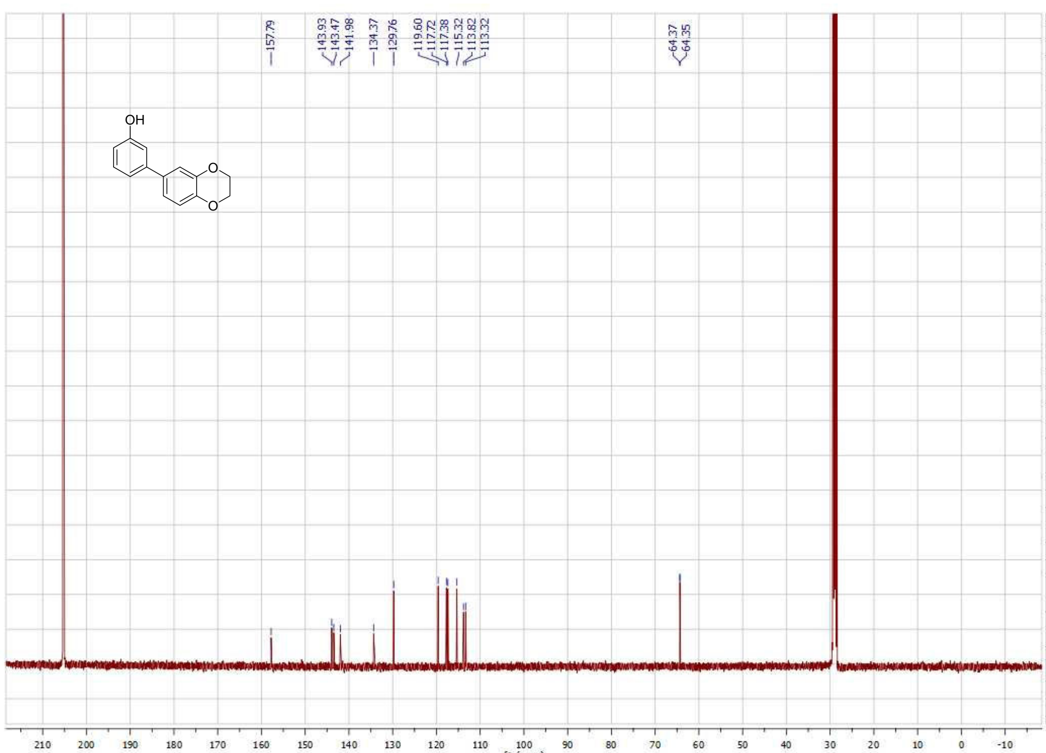
^{13}C NMR of (**A-3**)



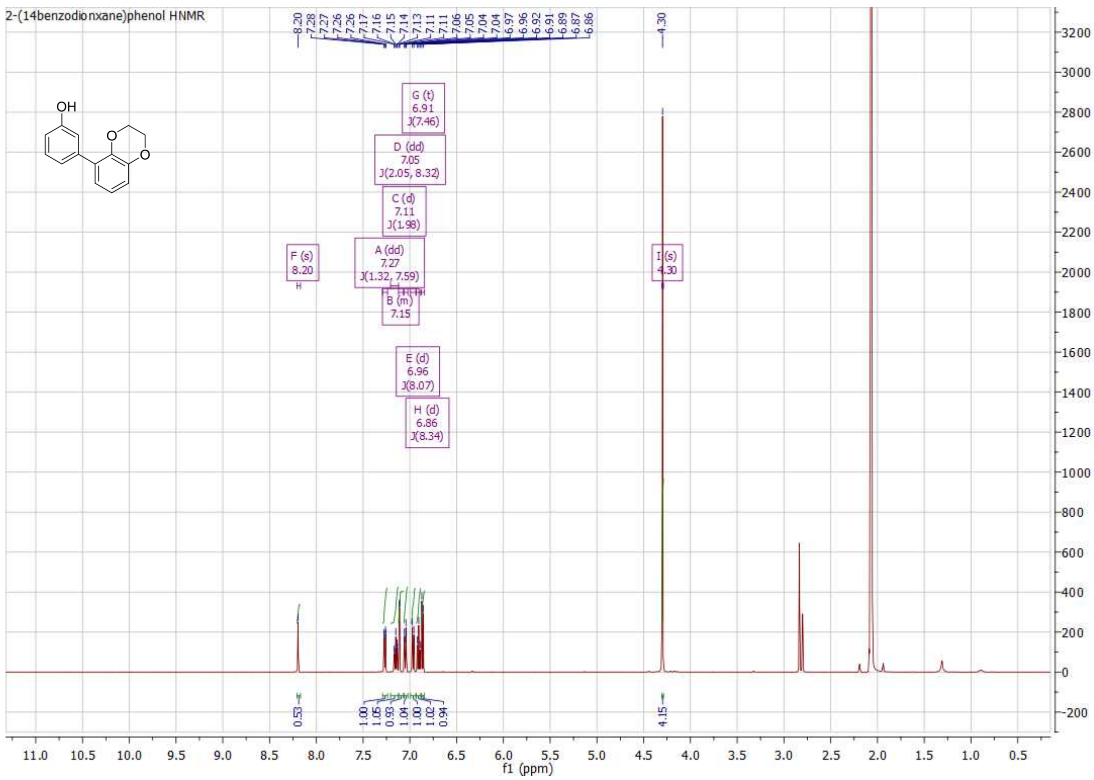
^{1}H NMR of (**A-5**)



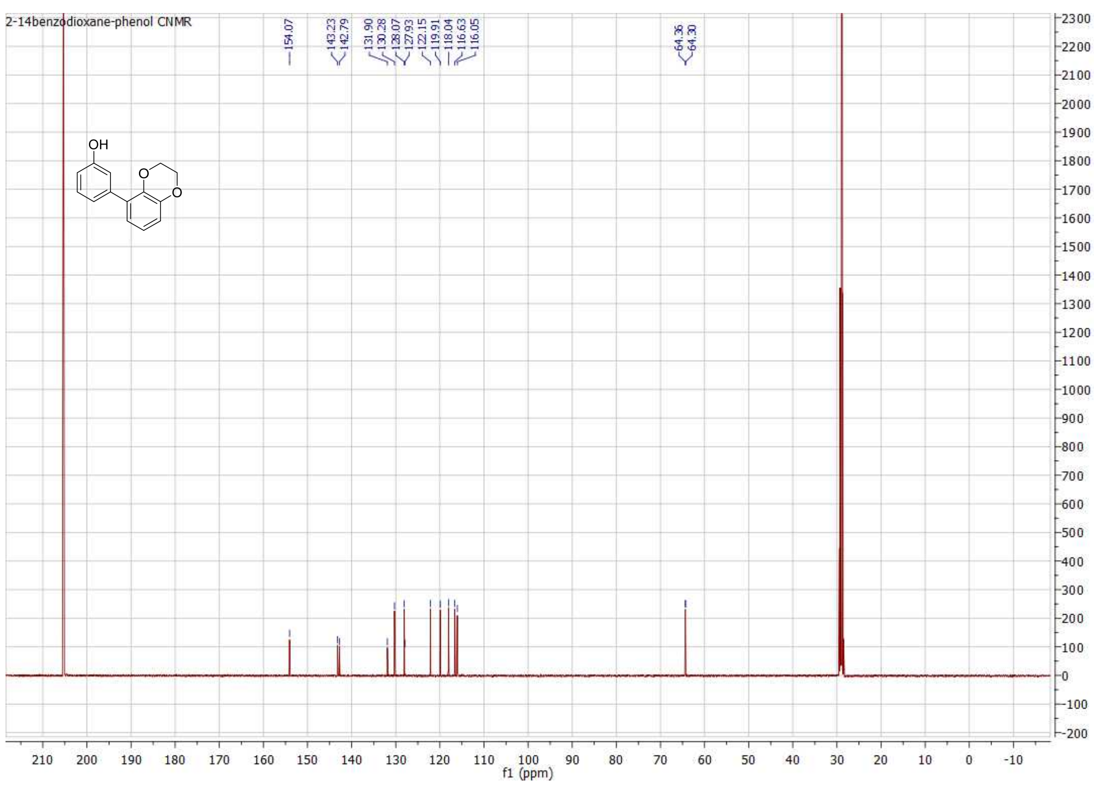
^{13}C NMR of (**A-5**)



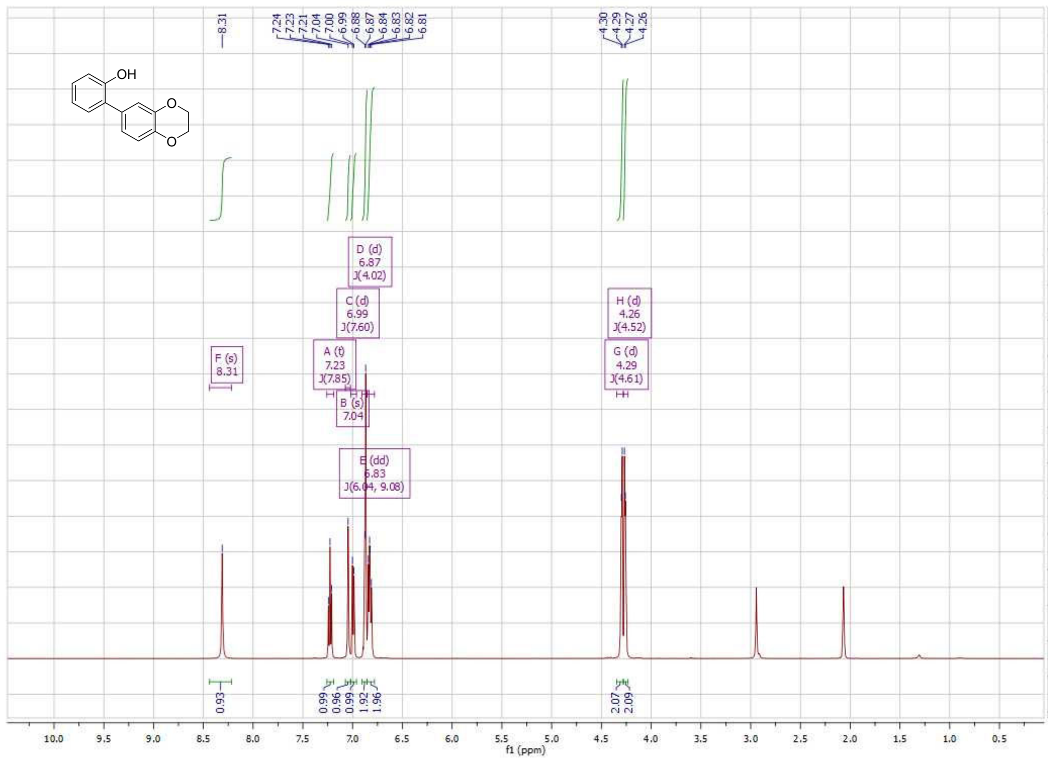
^{1}H NMR of (**A-6**)



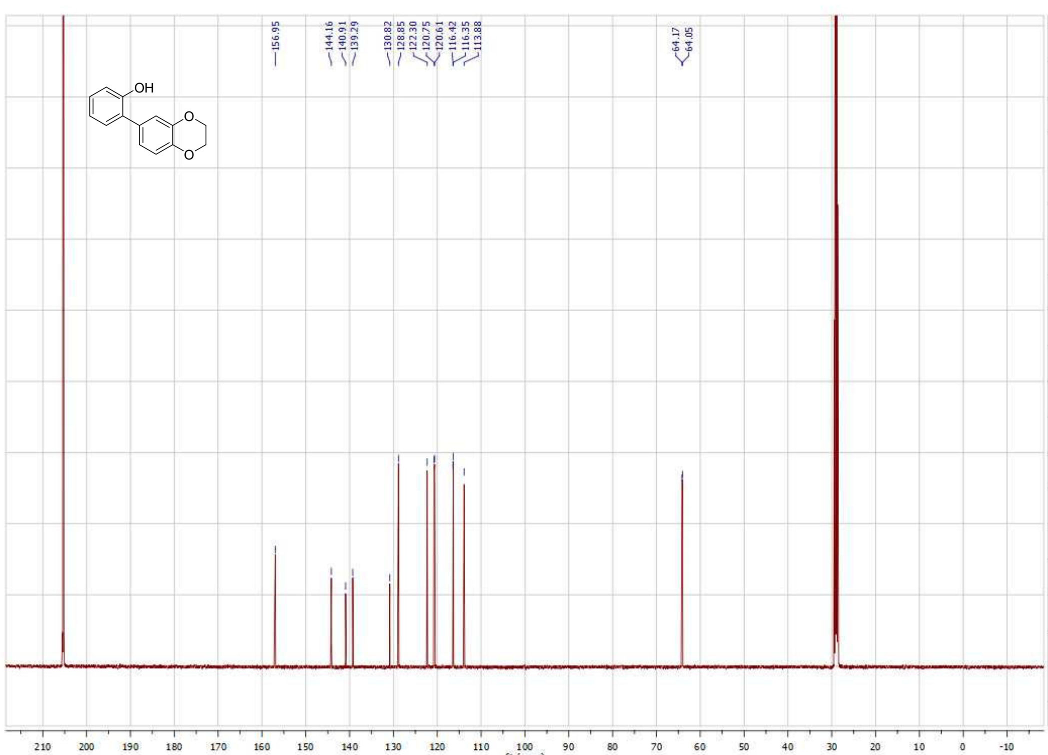
^{13}C NMR of (**A-6**)



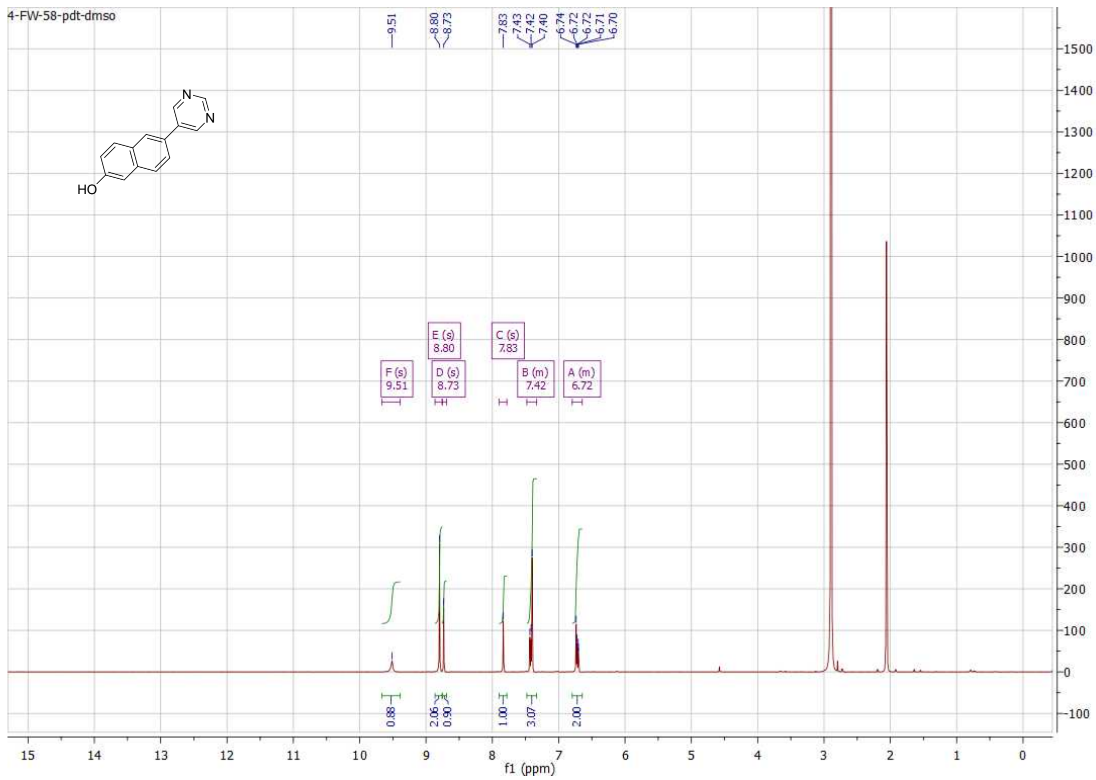
[1]H NMR of (**A-7**)



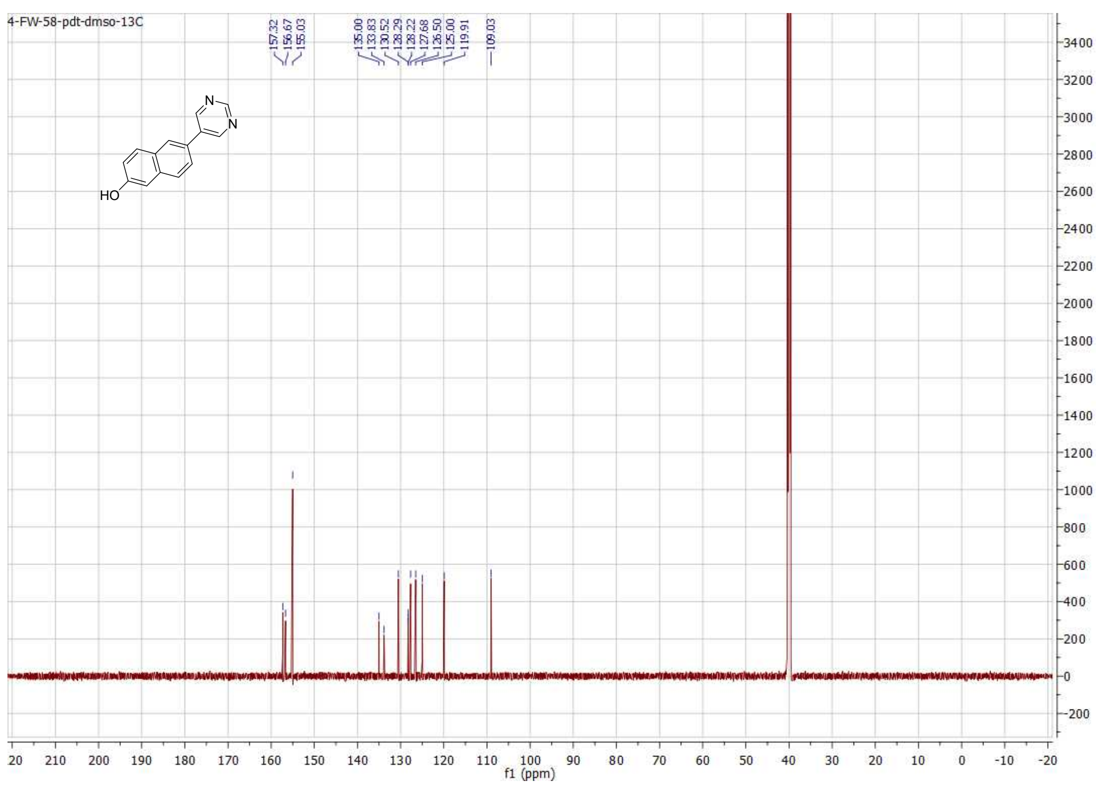
[13]C NMR of (**A-7**)



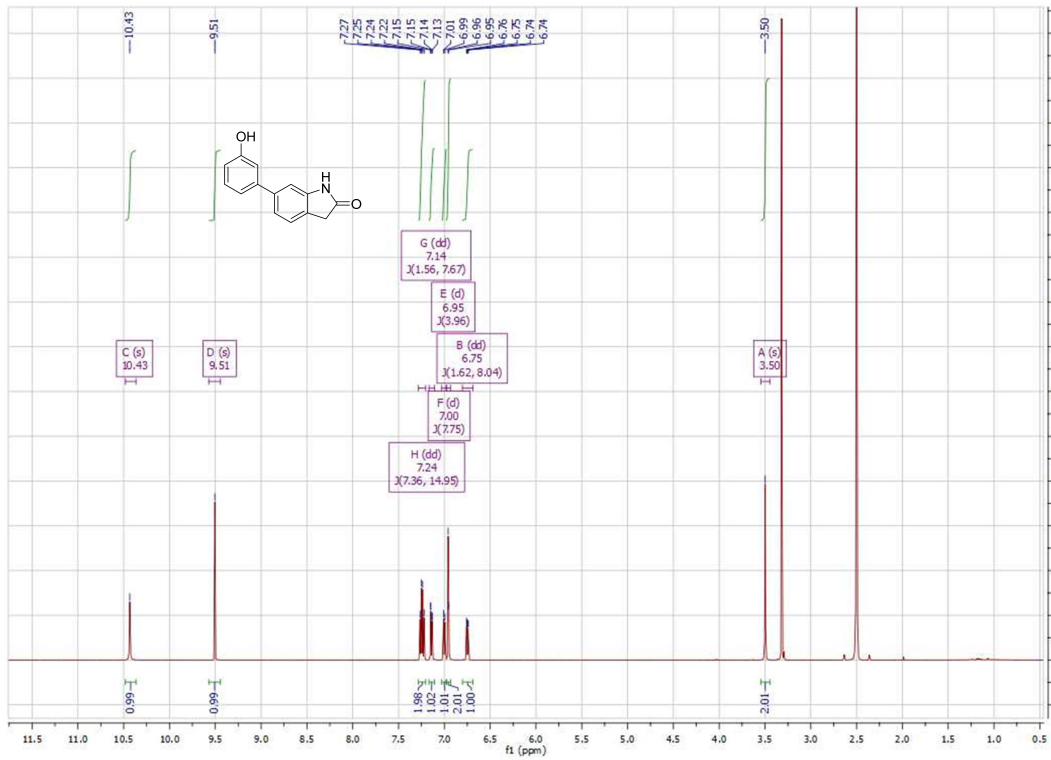
^{1}H NMR of (**A-8**)



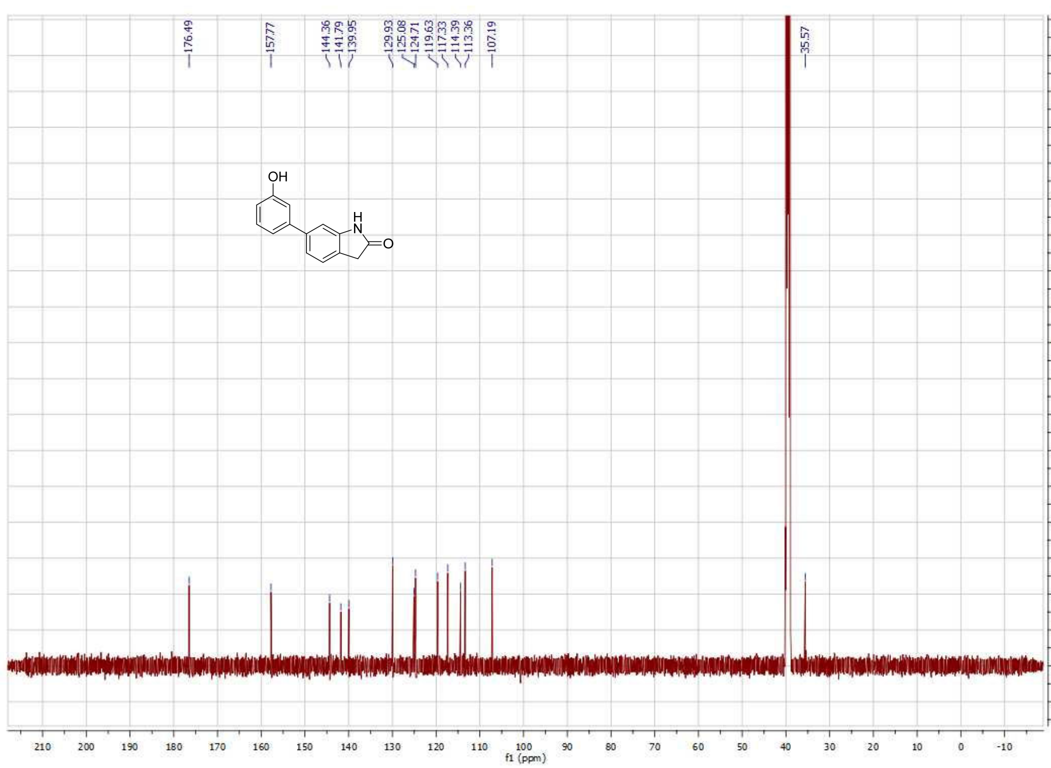
^{13}C NMR of (**A-8**)



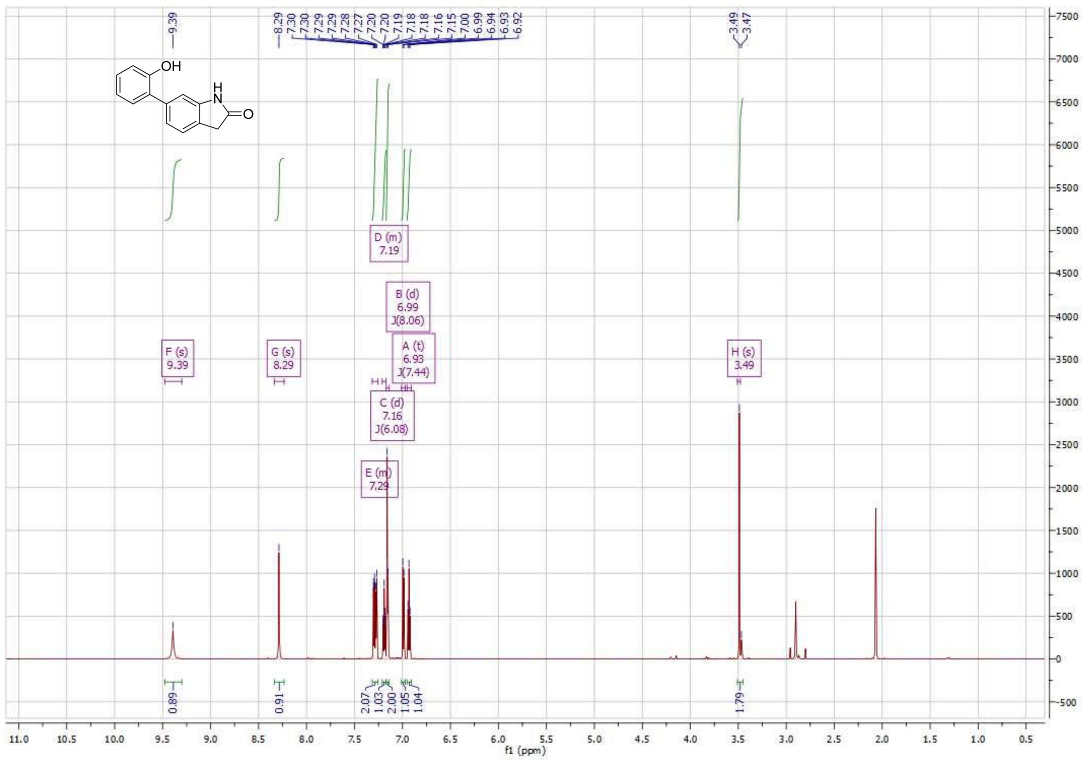
[1]H NMR of (**A-13**)



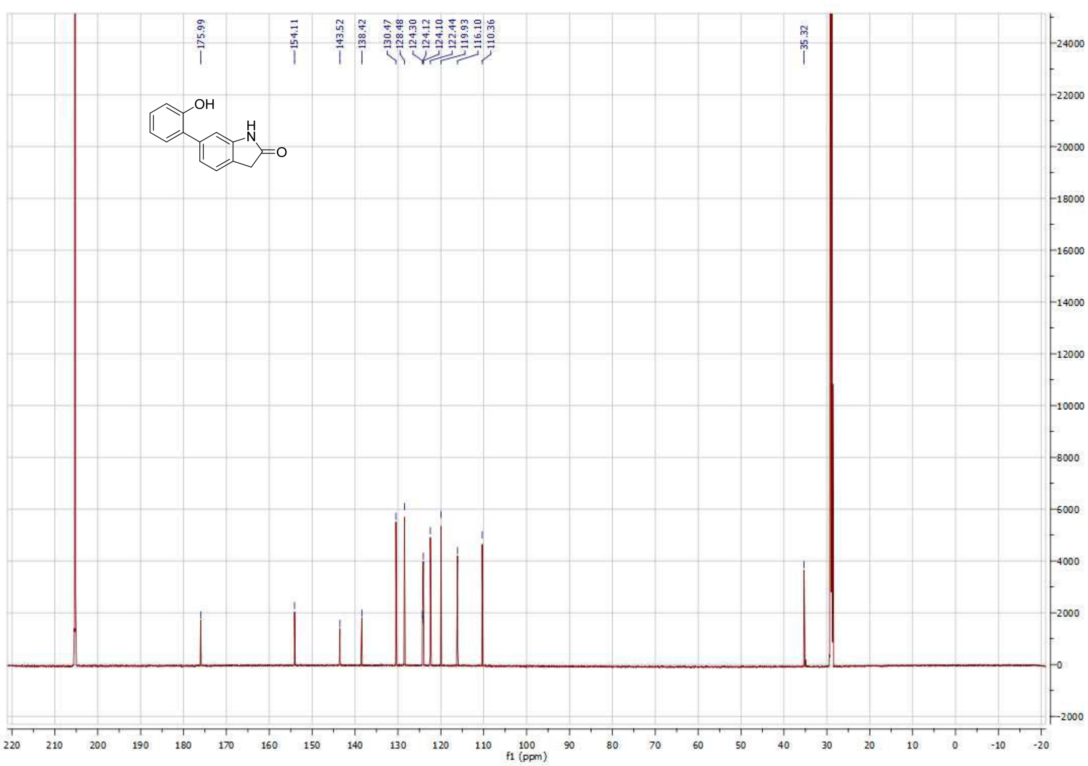
[13]C NMR of (**A-13**)



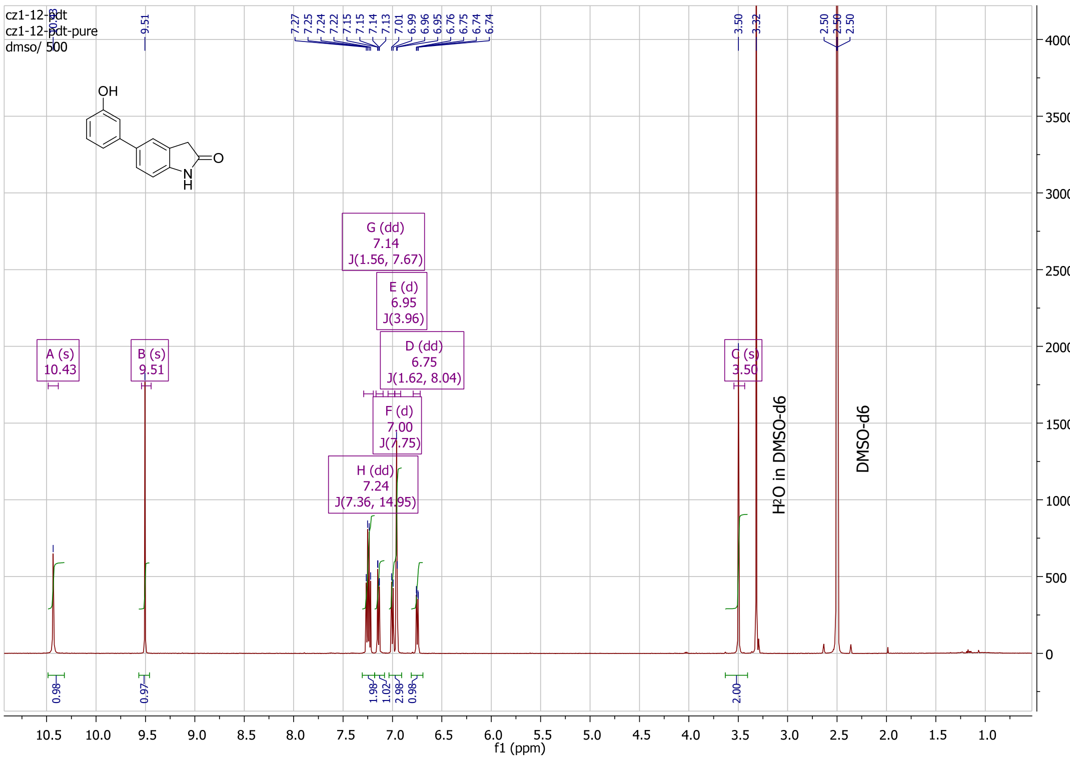
^{1}H NMR of (**A-14**)



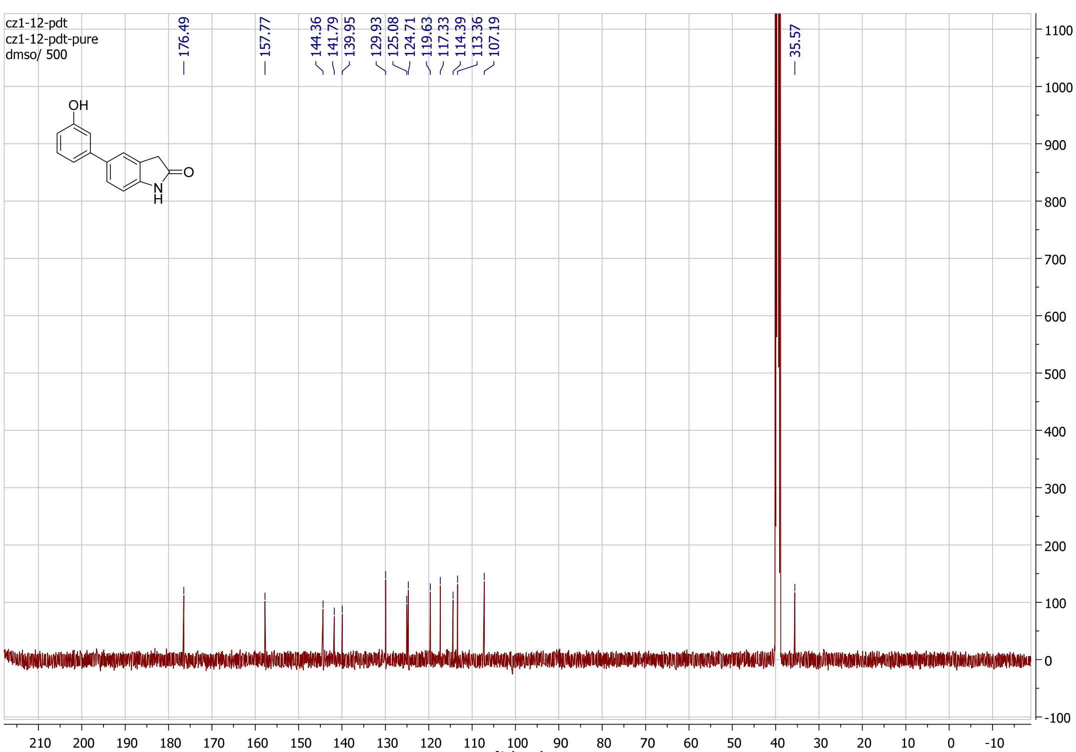
^{13}C NMR of (**A-14**)



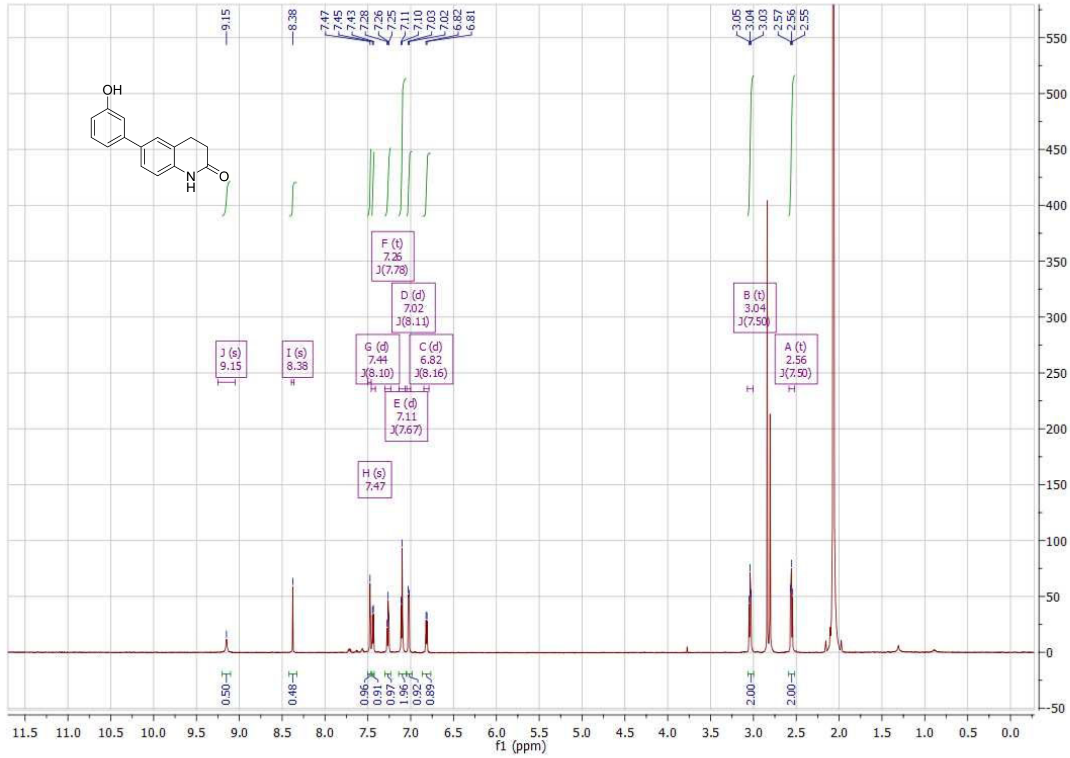
^{1}H NMR of (**A-15**)



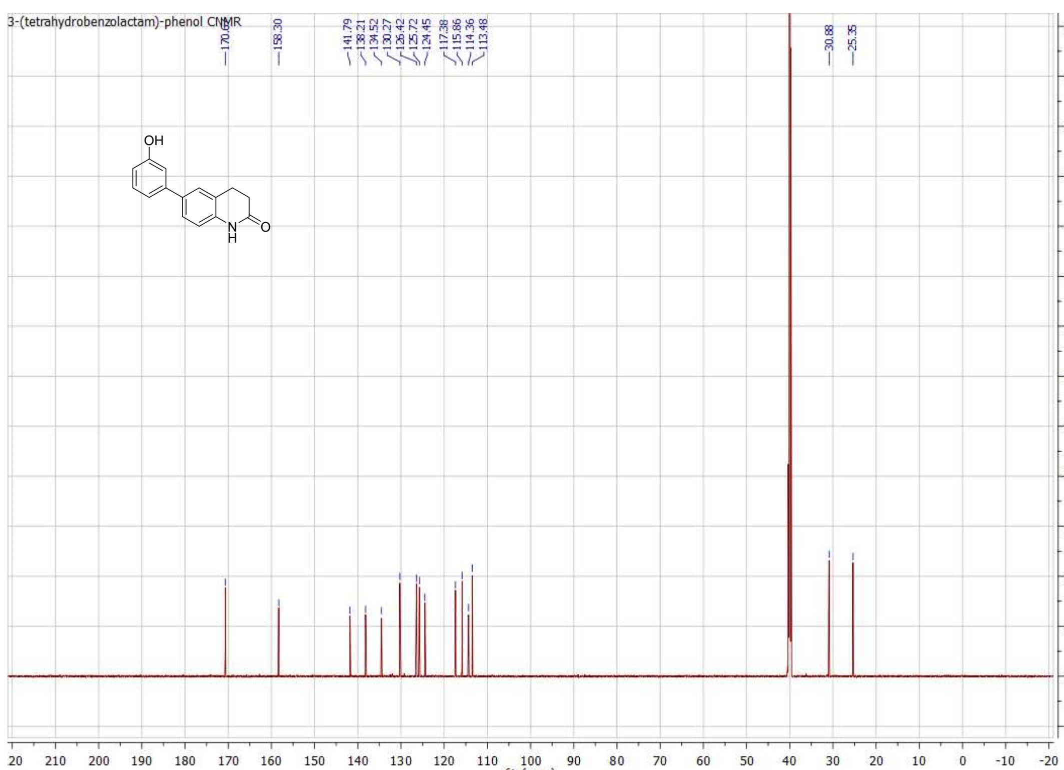
^{13}C NMR of (**A-15**)



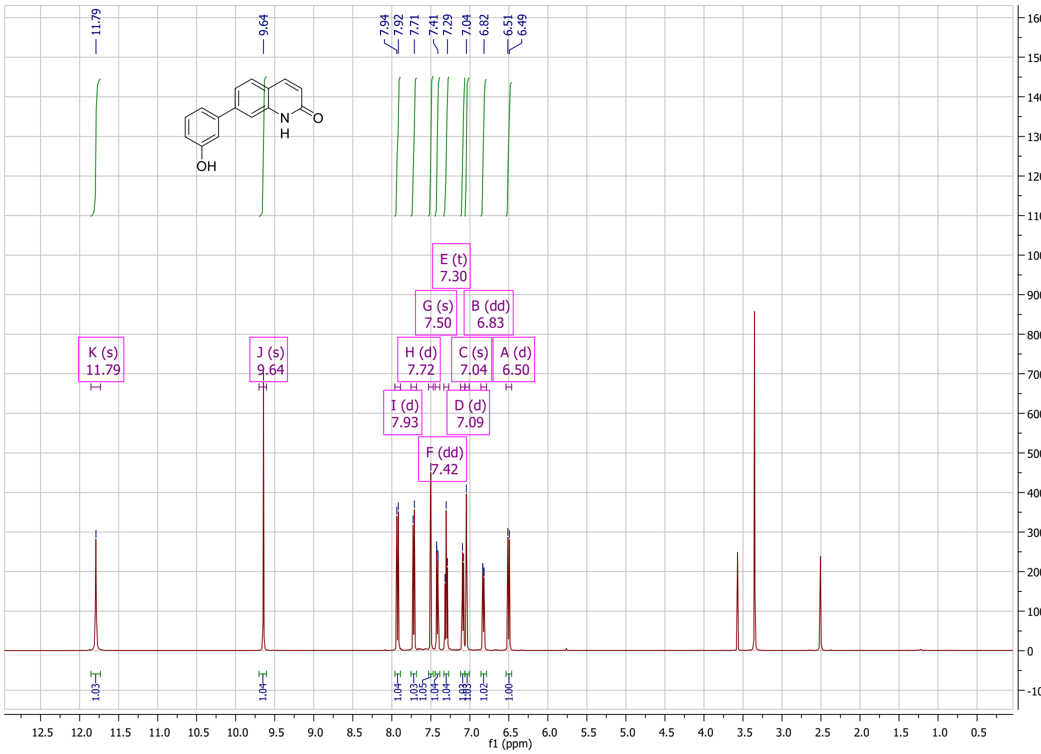
[1]H NMR of (**A-16**)



[13]C NMR of (**A-16**)



^{1}H NMR of (**A-17**)



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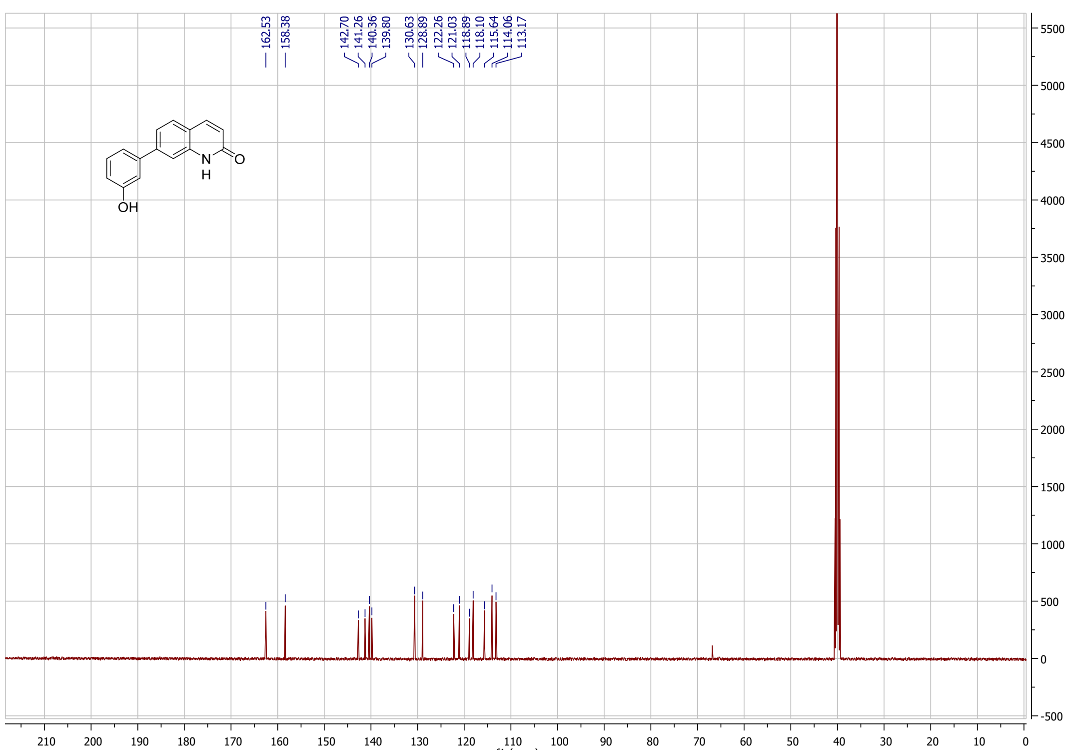
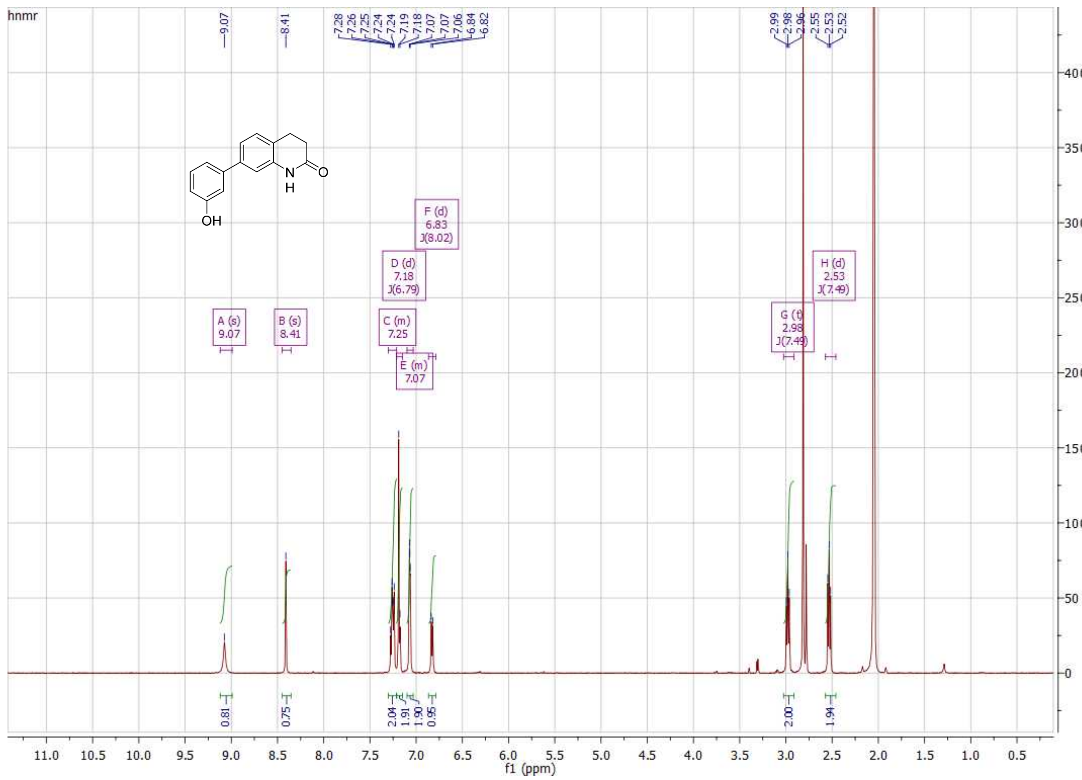
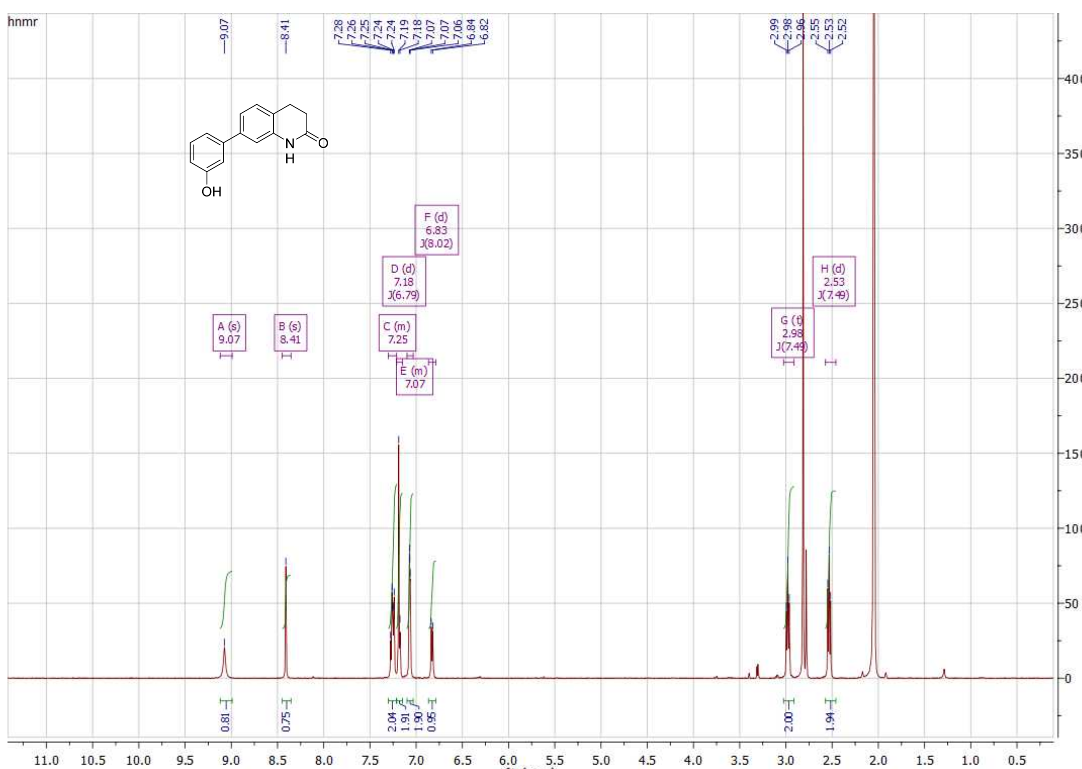
^{13}C NMR of (**A-17**)



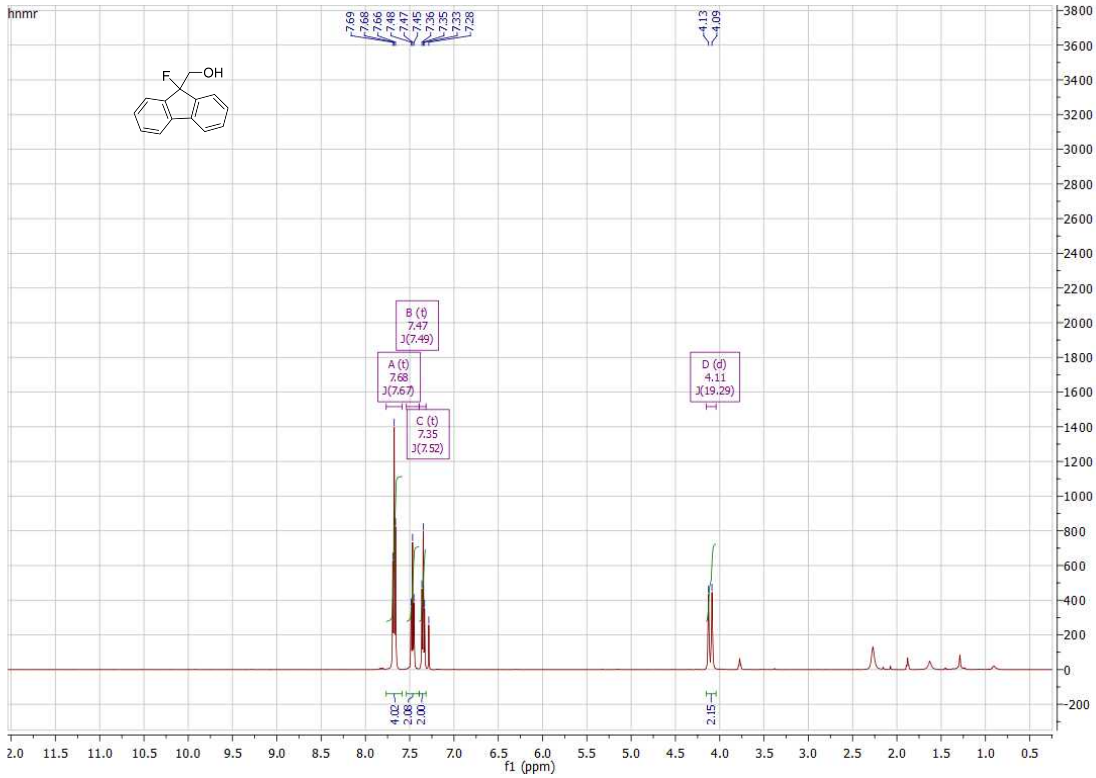
^{1}H NMR of (**A-18**)



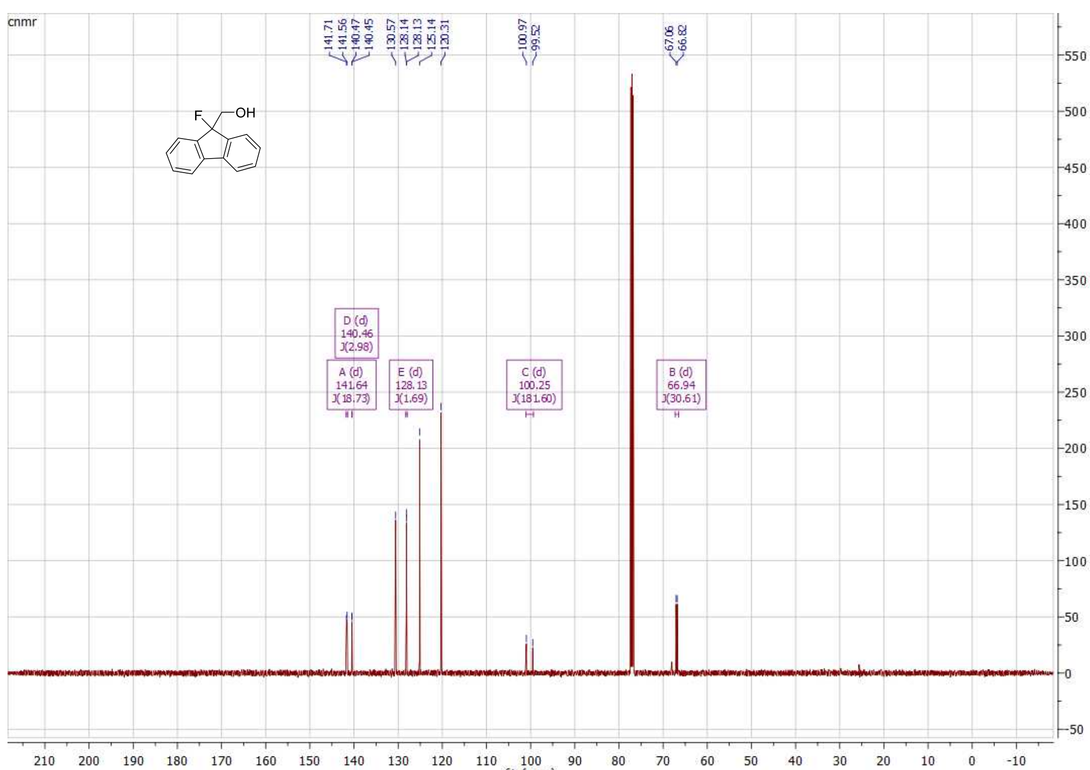
^{13}C NMR of (**A-18**)



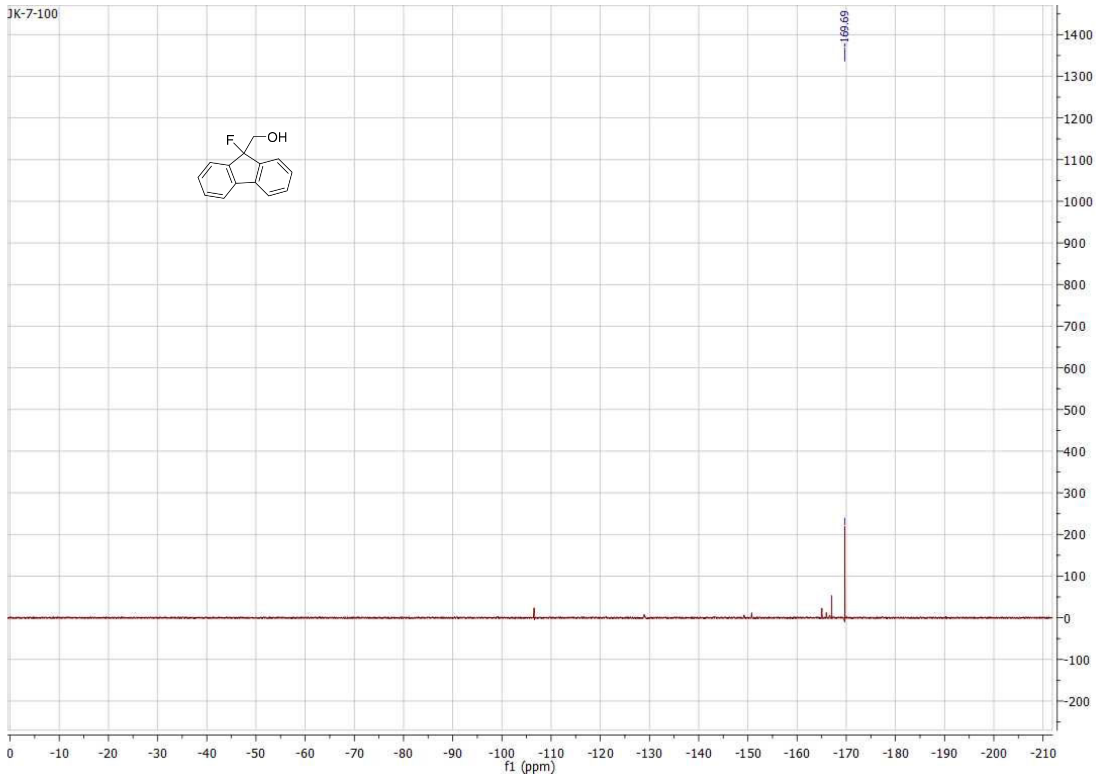
^{1}H NMR of (**A-19**)



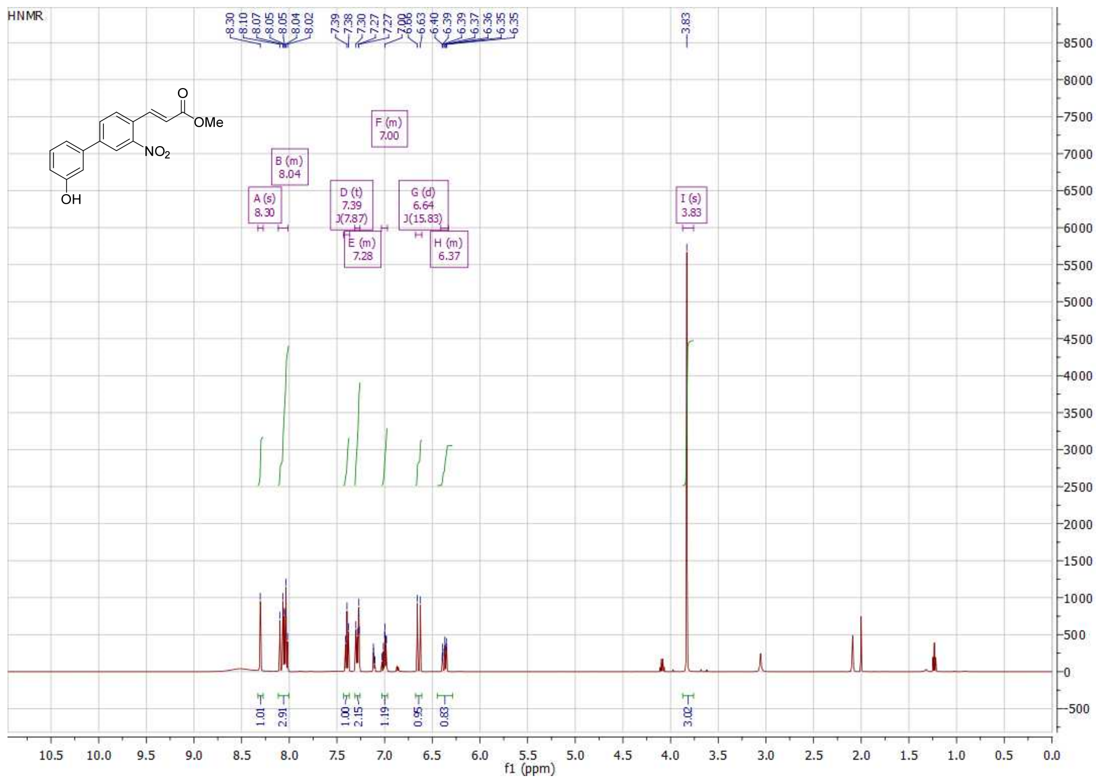
^{13}C NMR of (**A-19**)



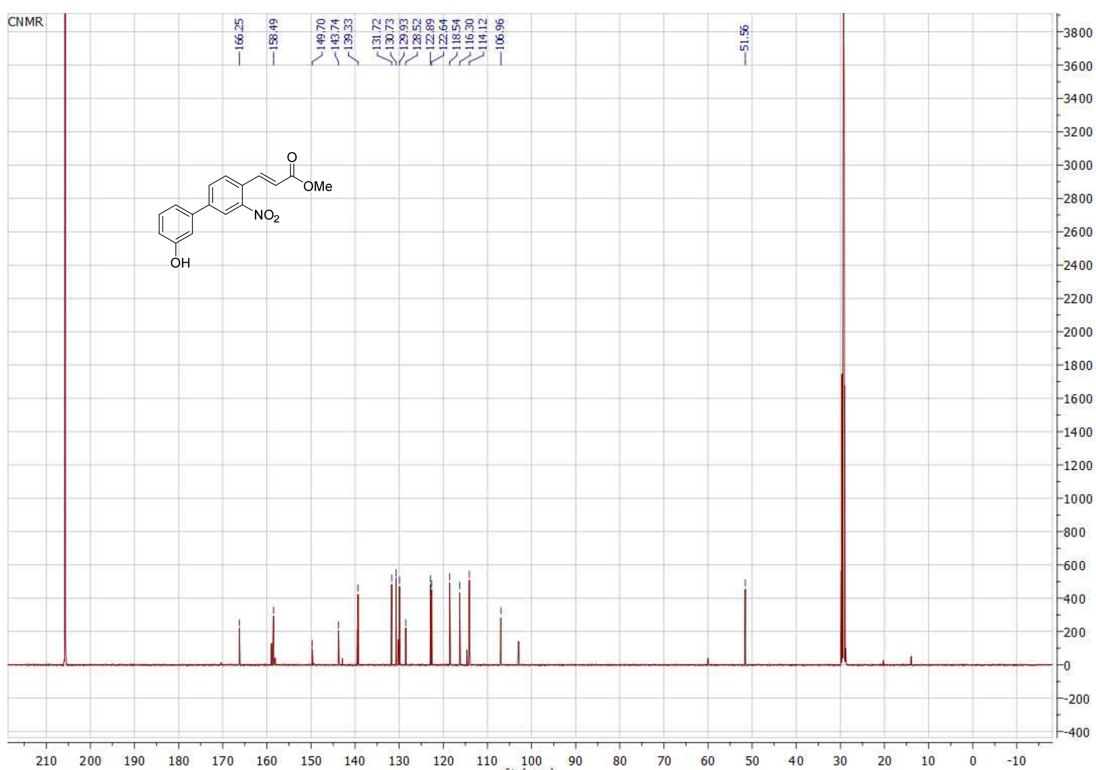
^{19}F NMR of (**A-20**)



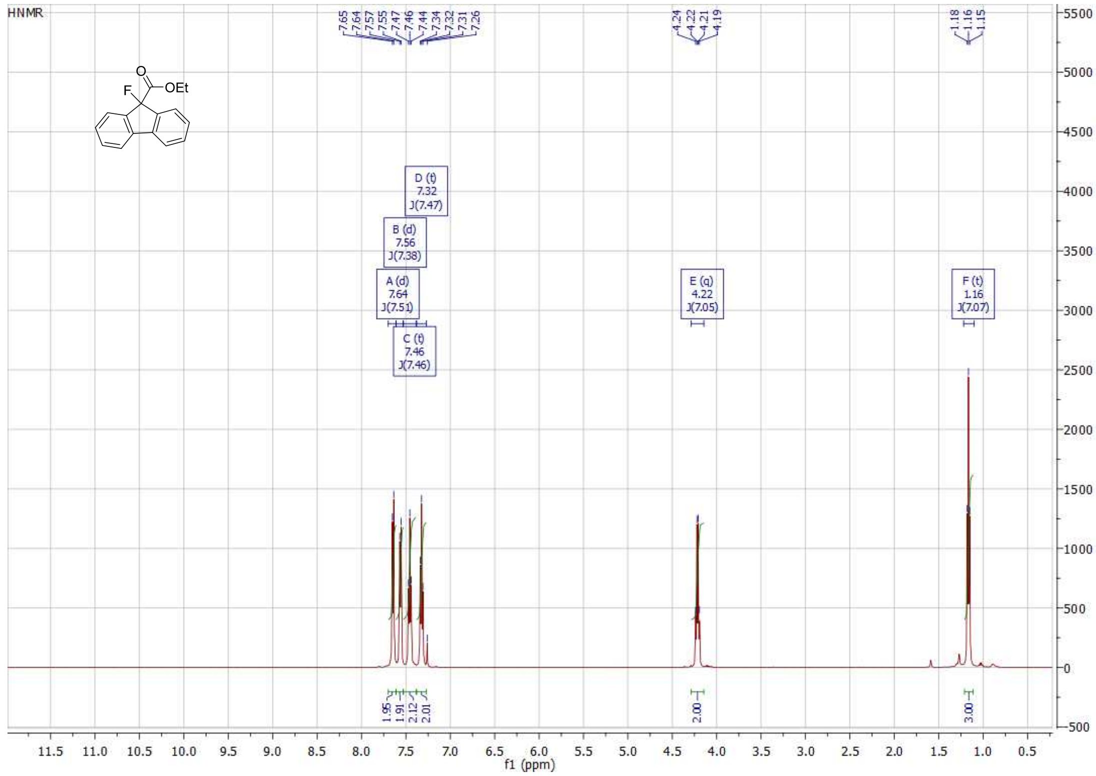
^{1}H NMR of (**B-3**)



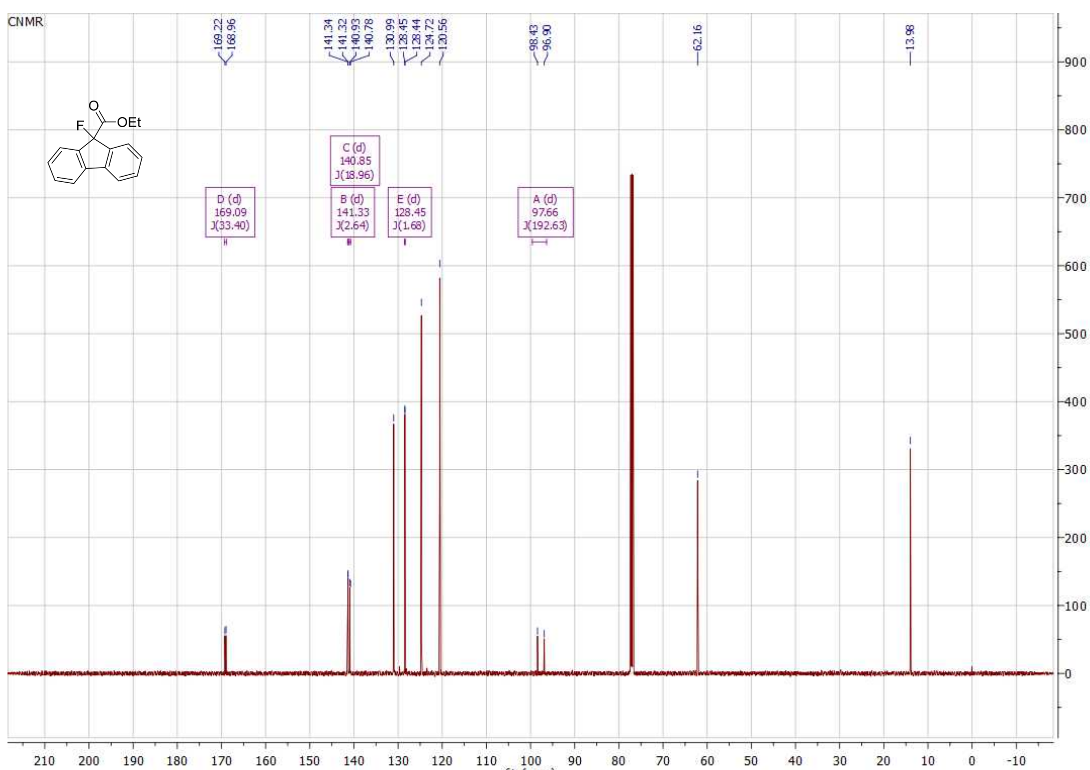
^{13}C NMR of (**B-3**)



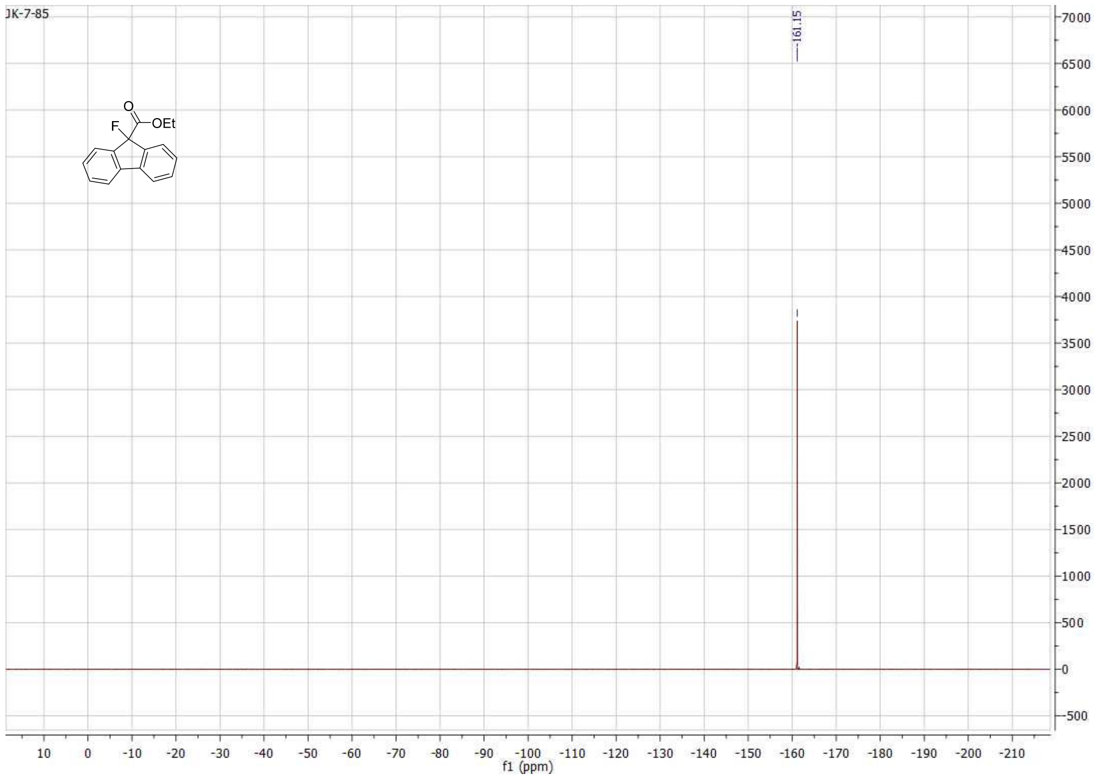
[1]H NMR of (**B-5**)



[13]C NMR of (**B-5**)

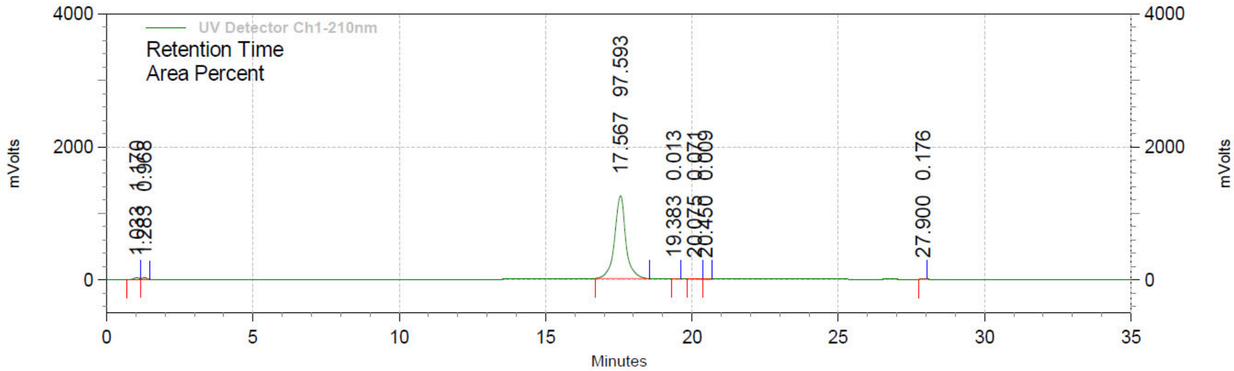


^{19}F NMR of (**B-5**)


JK-7-85
-161.15
O
F
OEt
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)

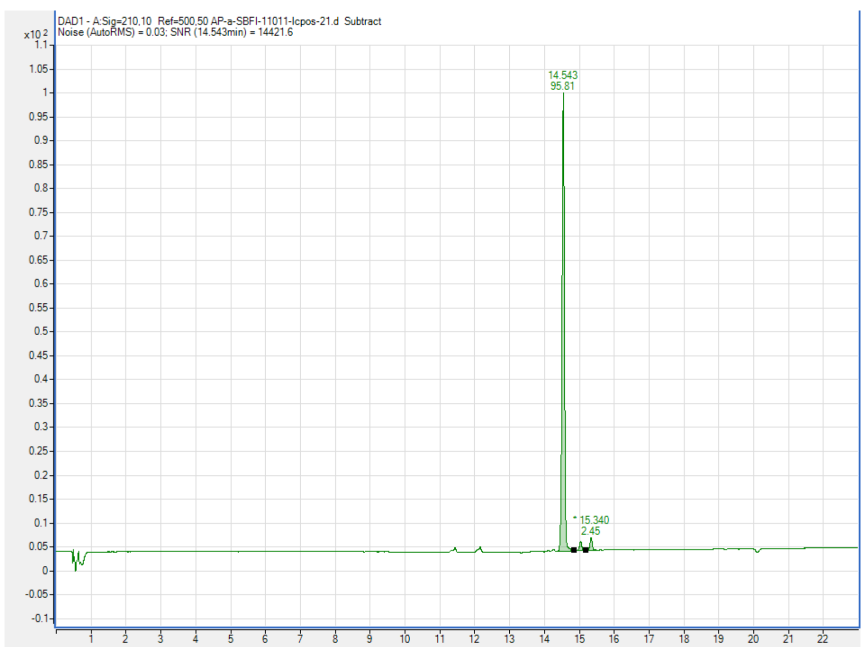
HPLC purities of the five compounds examined *in vivo*

(1) **α-1** (97.6%)



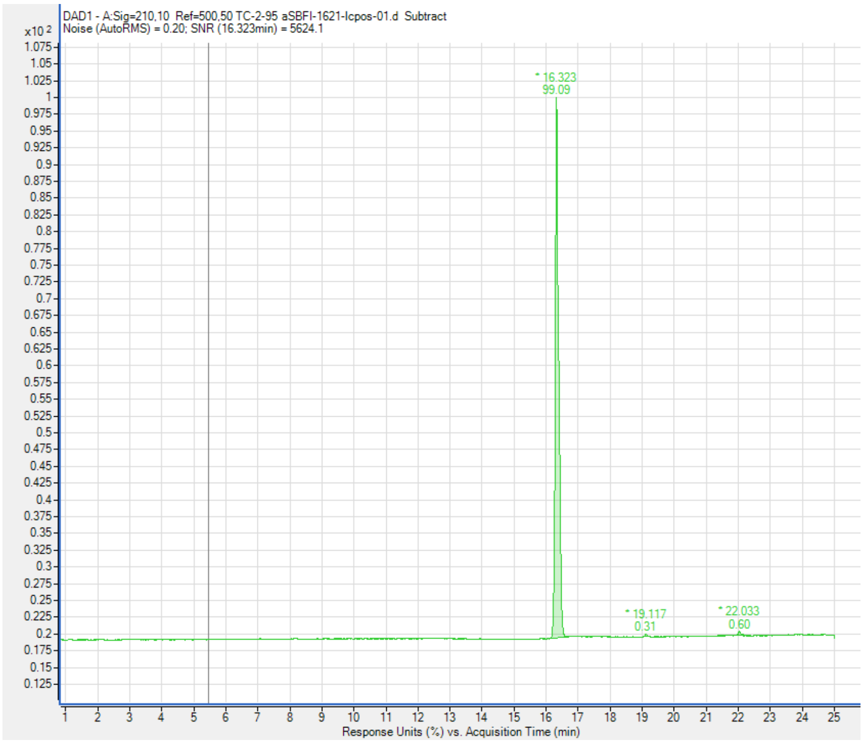
Condition (5) (Shimadzu LC-2010A): Kinetex F5, 2.6 µm, 100 Å, 100 x 4.6 mm column, solvent A: H_2O, solvent B: CH_3CN, flow rate:1.0 mL/min, t: 0-35 min, gradient: 5-95% solvent B, 25 ℃.

(2) **α-4** (95.8%)



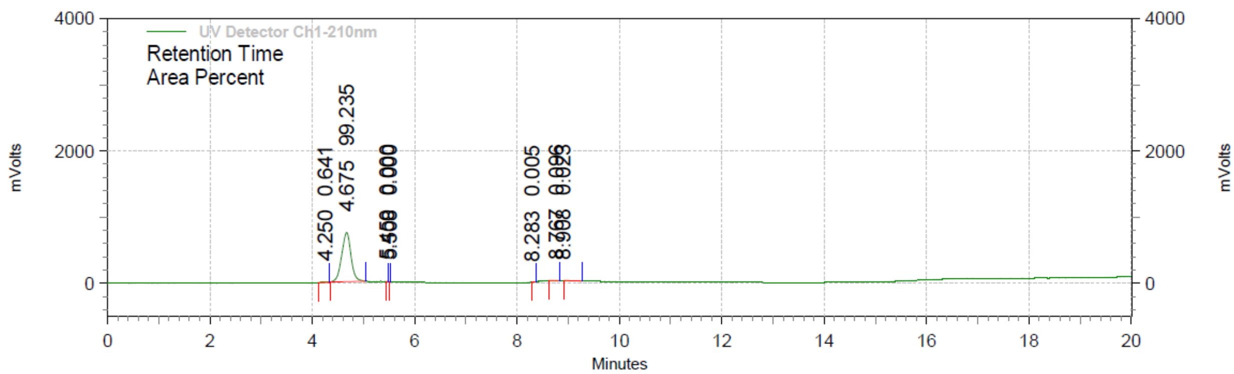
Condition (1) (Agilent 1100): Kinetex evoc18, 2.6 µm, 100 Å, 100 x 2.1 mm column, solvent A: H_2O (5 mM ammonium acetate, pH 7), solvent B: CH_3CN/H_2O, 9:1 (5 mM ammonium acetate, pH 7), flow rate: 0.50 mL/min, t: 0-30 min, gradient: 5-100% solvent B, 45 ℃.

(3) **α-16** (99.1%)



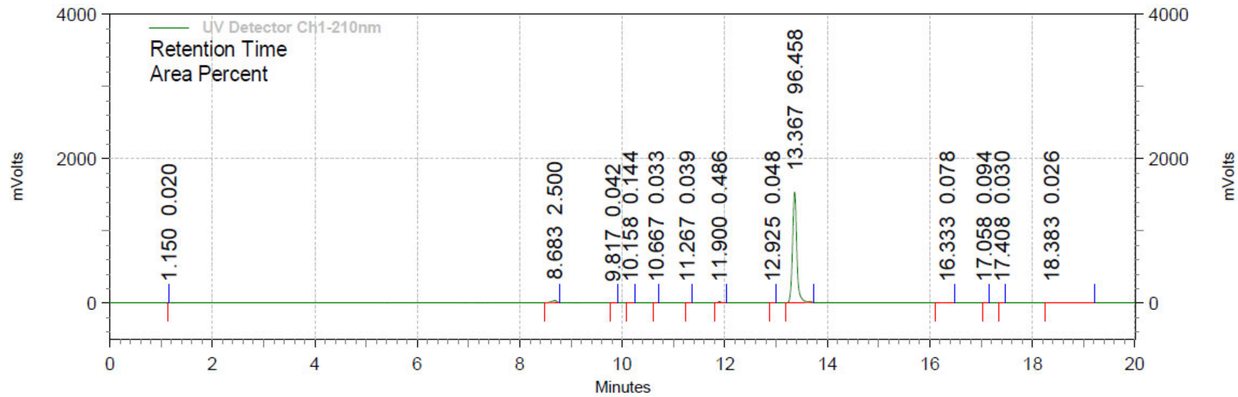
Condition (2) (Agilent 1100): Kinetex F5, 2.7 µm, 100 Å, 100 x 2.1 mm column, solvent A: H_2O (10 mM ammonium acetate), solvent B: CH_3CN/H_2O, 95:5 (10mM ammonium acetate), flow rate: 0.50 mL/min, t: 0-46 min, gradient: 5-95% solvent B, 45 °C.

(4) **γ-3** (99.2%)



Condition (5) (Shimadzu LC-2010A): Kinetex F5, 2.6 µm, 100 Å, 100 x 4.6 mm column, solvent A: H_2O, solvent B: CH_3CN, flow rate:1.0 mL/min, t: 0-20 min, gradient: 5-95% solvent B, 25 °C.

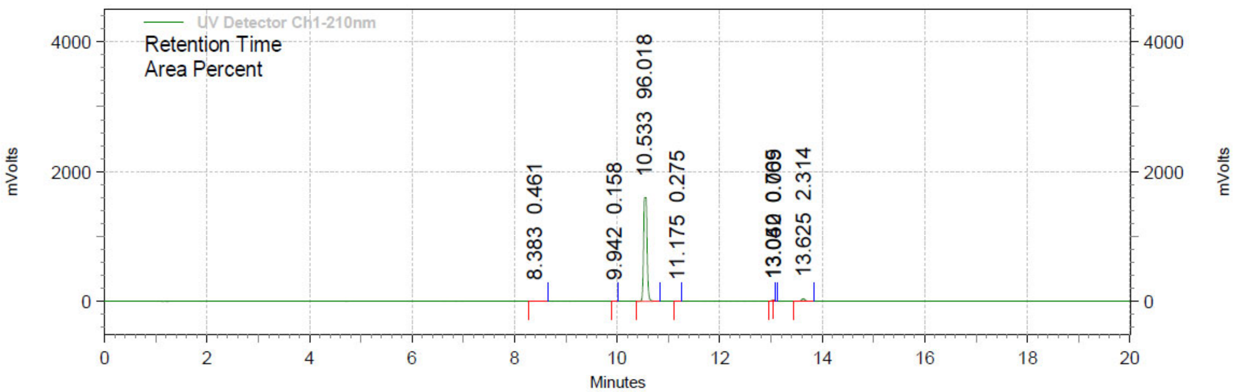
(5) **γ-9** (96.5%)



Condition (5) (Shimadzu LC-2010A): Kinetex F5, 2.6 μm, 100 Å, 100 x 4.6 mm column, solvent A: H_2O, solvent B: CH_3CN, flow rate:1.0 mL/min, t: 0-20 min, gradient: 5-95% solvent B, 25 ℃.

Examples of the HPLC purities of other compounds examined *in vitro* for affinities to FABP3, 5 and 7

α-3 (96.0%)

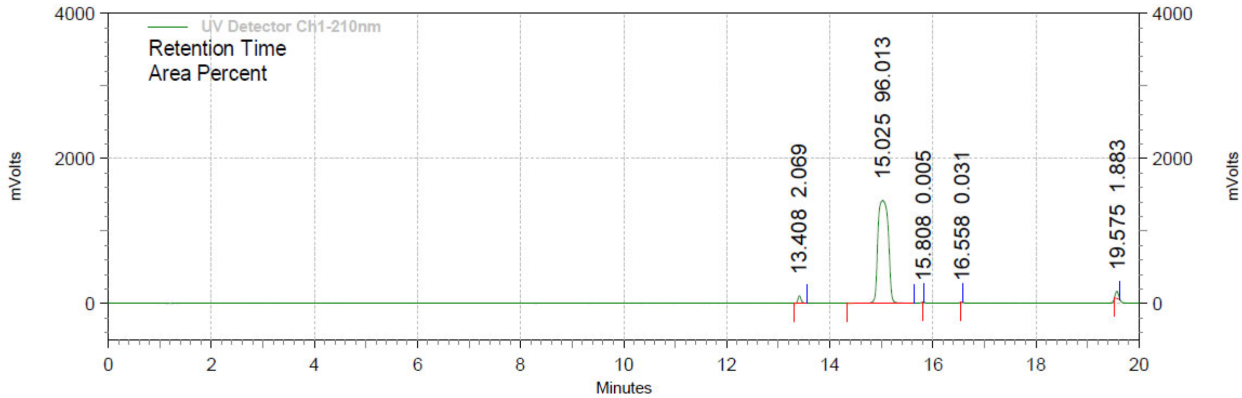


Condition (5) (Shimadzu LC-2010A): Kinetex F5, 2.6 µm, 100 Å, 100 x 4.6 mm column, solvent A: H_2O, solvent B: CH_3CN, flow rate:1.0 mL/min, t: 0-20 min, gradient: 5-95% solvent B, 25 ℃.

α-6 (99.0%)

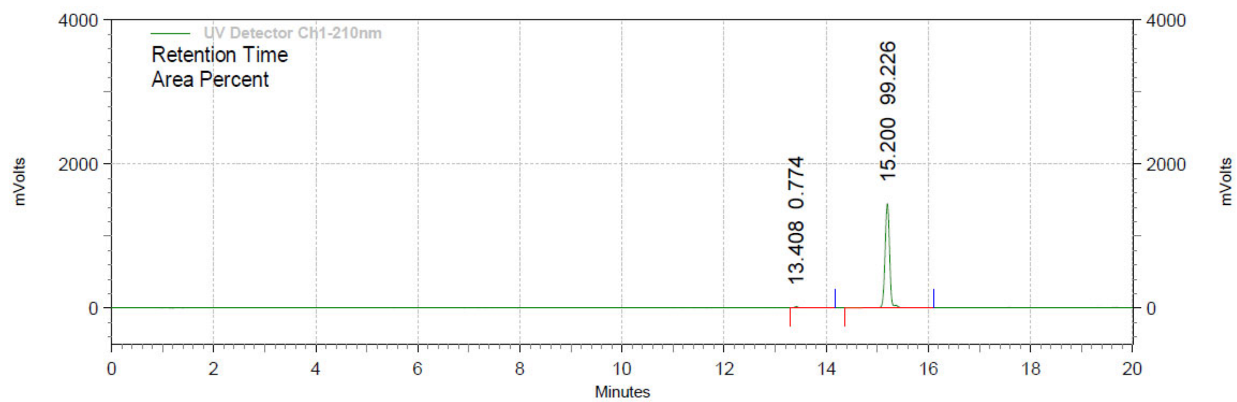
Conditions (1) (Agilent 1100): Kinetex evoc18, 2.6 µm, 100 Å, 100 x 2.1 mm column, solvent A: H_2O (5 mM ammonium acetate, pH 7), solvent B: CH_3CN/H_2O, 9:1 (5 mM ammonium acetate, pH 7), flow rate: 0.50 mL/min, t: 0-30 min, gradient: 5-100% solvent B, 45 ℃.

α-TAMSE-1 (96.0%)



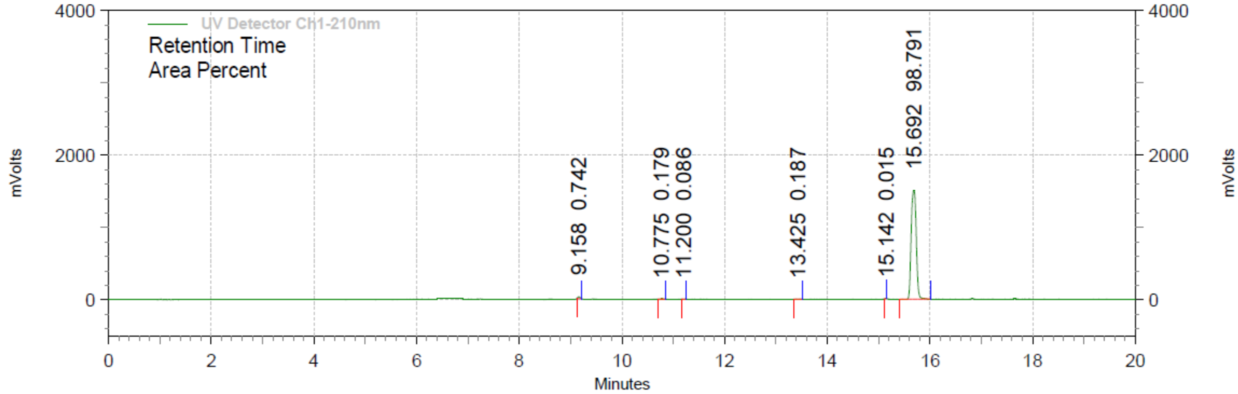
Condition (5) (Shimadzu LC-2010A): Kinetex F5, 2.6 µm, 100 Å, 100 x 4.6 mm column, solvent A: H_2O, solvent B: CH_3CN, flow rate:1.0 mL/min, t: 0-20 min, gradient: 5-95% solvent B, 25 °C.

α-2-MeO-TAMSE-1 (99.2%)



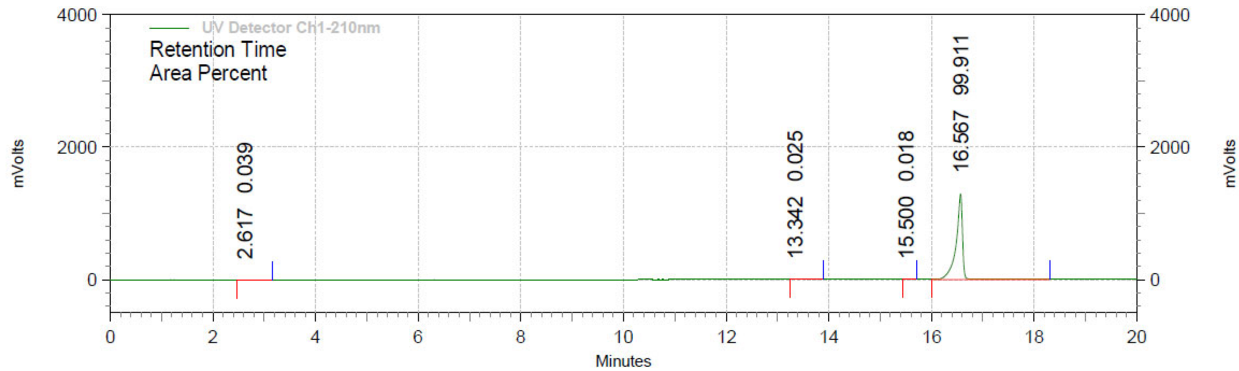
Condition (5) (Shimadzu LC-2010A): Kinetex F5, 2.6 µm, 100 Å, 100 x 4.6 mm column, solvent A: H_2O, solvent B: CH_3CN, flow rate:1.0 mL/min, t: 0-20 min, gradient: 5-95% solvent B, 25 °C.

α-TAMSE-2 (98.8%)



Condition (5) (Shimadzu LC-2010A): Kinetex F5, 2.6 µm, 100 Å, 100 x 4.6 mm column, solvent A: H_2O, solvent B: CH_3CN, flow rate:1.0 mL/min, t: 0-20 min, gradient: 5-95% solvent B, 25 ℃.

ε-202 (99.9%)



Condition (5) (Shimadzu LC-2010A): Kinetex F5, 2.6 µm, 100 Å, 100 x 4.6 mm column, solvent A: H_2O, solvent B: CH_3CN, flow rate:1.0 mL/min, t: 0-20 min, gradient: 5-95% solvent B, 25 ℃.