

SUPPORTING INFORMATION

Discovery of new chiral sulfonamides bearing benzoxadiazole as HIF inhibitors for non-small cell lung cancer therapy: design, microwave-assisted synthesis, binding affinity, *in vitro* antitumoral activities and *in silico* studies

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MOLECULAR DOCKING

MAATTANPEMTSDVPSLGPAlASGNSGPGIQGGGAIVQRAIKRRPGLDFDDDGEGN SKFLRCDDDQMSNDKERFARS DDEQSSADKER
LARENHSEIERRRNKMTAYITELSDMVPTCSALARKPDKLTLRMAVSHMKSLRG TGNTSTDSYKPSFLTDQELKHLILEAADGFLFI
VSCETGRVVYVSDSVTPVLNQPQSEWFGSTLYDQVHPDDVDKLREQLSTSENALTGRILD LKTGTVKKEGQQSSMRMCMGSRRSFICR
MRCGSSSVDPVS VNR LS FVRNRCRN GLGSVKDGE PHFVVVHCTGYIKAWPPAGVSLPDDPEAGQGS KFC LVAIGRLQVTSSPNCTDM
SNVCQPTEFISRH NIEGIFTFVDHRCVATVG YQPQELLGKNIVEFCH PEDQQLRDSFQQVVKLGQVLSVMFRFRSKNQE WLWMRTSS
FTFQN PYSDEIEYI I CTNTNVKNSSQEP RPLS NTIQR PQLGPTANLPLEM GSGQLAPRQQQQTE LD MVPG RDGLASYNHSQVV QPVTT
TGPEHSKPLEKSDGLFAQDRDPRFSEIYHNINADQSKGISSSTVPATQQLFSQGNTFPPTPRPAENFRNSGLAPPVTIVQPSASAGQMLAQI
SRHSNPTQGATPTWTPTTRSGFSAQQVATQATAKRTSQFGVGSFQTPSSSMSLPGAPTASPGAA YPSLTNRGSNFAPETGQTAGQ
FQTRTAEGVGVWPQWQQPHRSSSEQHVQQPPAQQPGQPEVFQEMLSGDQSNSYNNEFPDLTMFPFSE

Figure S1. Amino acid sequence of the recombinant Human ARNT, GST-tagged.



Figure S2. Three-dimensional model structures of HIF-1 β

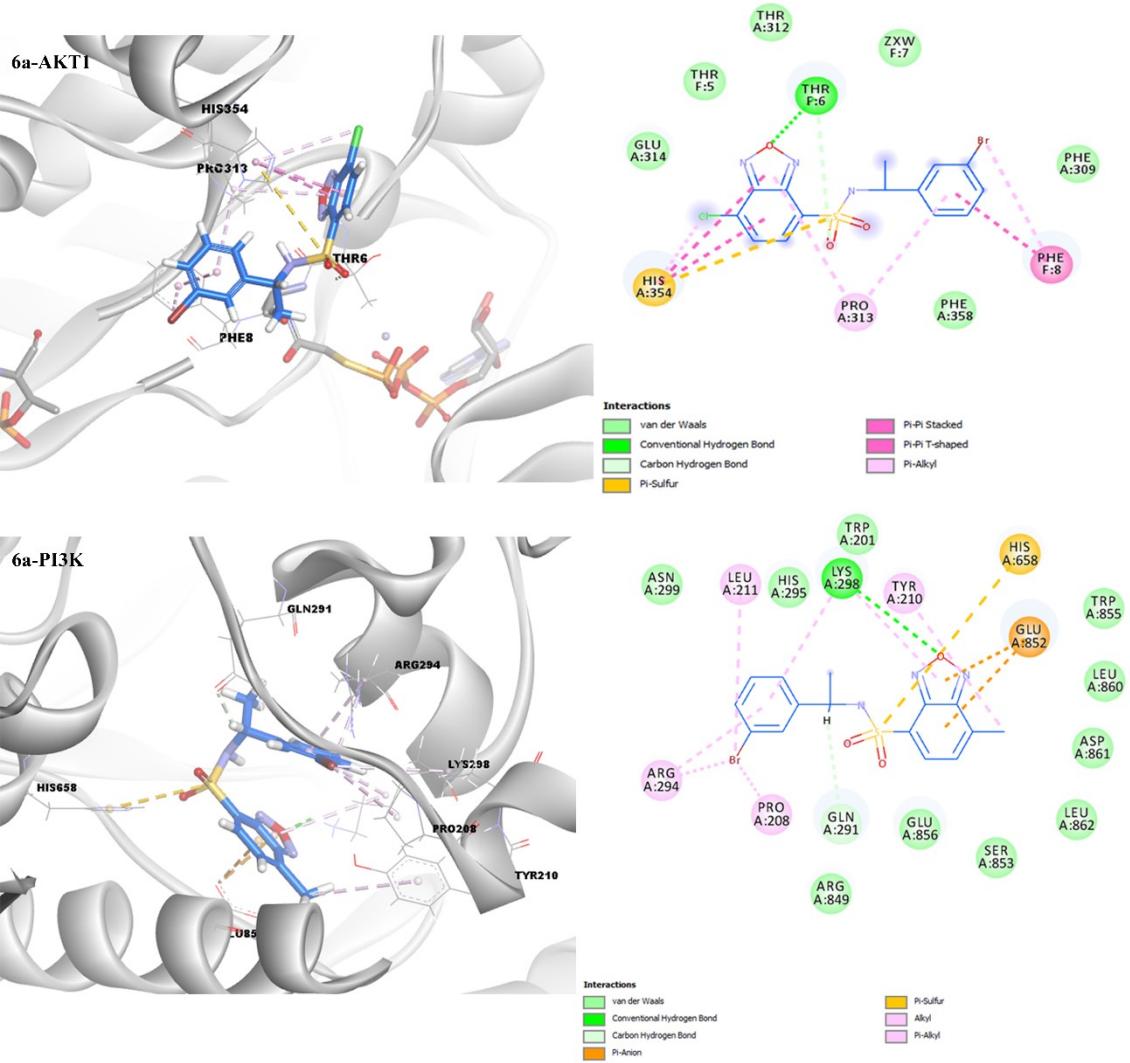


Figure S3. 2D and 3D docking poses of 6a compound with AKT1 and PI3K.

Table S1. The model scores of HIF-1 β sequence. The best model was defined as red color in the Table.

Model Scores			
Name	PDF Total Energy	PDF Physical Energy	DOPE Score
HIF1beta.M0002	1715.5006	926.995288999999	-31050.287109
HIF1beta.M0003	1723.1072	913.212591900001	-31007.003906
HIF1beta.M0007	1765.3840	938.180720199998	-31037.191406
HIF1beta.M0006	1857.9734	934.64224648	-30742.488281
HIF1beta.M0005	1873.5293	951.290318999999	-30286.593750
HIF1beta.M0001	1947.4524	937.011126019999	-30951.626953
HIF1beta.M0004	2043.2388	975.618102150001	-30929.406250
HIF1beta.M0010	2313.1152	962.969619	-30320.083984
HIF1beta.M0009	2354.1763	983.148584700001	-30492.878906
HIF1beta.M0008	3741.2090	1241.579581444	-30450.623047

Table S2. Validity of the potential model for HIF-1 β structure by using Profiles-3D. This model falls within the desired range.

Name	Verify Score	Verify Expected High Score	Verify Expected Low Score
HIF1beta.M0002	106.07	167.269	75.2712

Table.S3. Bonding interactions, bonding type and bonding distances of compounds **4b**, **6b**, **6a** and **7a** with HIF-1 β .

Interactions-4b	Distance Å	Bonding	Bonding Types	Binding site of enzyme	Binding site of ligand
:THR149:HN - :4b:O12	1.8540	Hydrogen Bond	Conventional Hydrogen Bond	:THR149:HN	:4b:O12
:THR146:HB - :4b:O13	2.3221	Hydrogen Bond	Carbon Hydrogen Bond	:THR146:HB	:4b:O13
:ASN148:HA - :4b:O12	2.2675	Hydrogen Bond	Carbon Hydrogen Bond	:ASN148:HA	:4b:O12
:4b:S11 - :TYR155	5.3371	Other	Pi-Sulfur	:TYR155	:4b:S11
:THR146:O - :4b	2.4309	Other	Pi-Lone Pair	:THR146:O	:4b
:LYS156:O - :4b	2.9946	Other	Pi-Lone Pair	:LYS156:O	:4b
:LYS156:O - :4b	2.5785	Other	Pi-Lone Pair	:LYS156:O	:4b
:TYR155 - :4b:CL34	3.5120	Hydrophobic	Pi-Alkyl	:TYR155	:4b:CL34
:GLY147:O - :4b:O13	2.9160	Unfavorable	Unfavorable Acceptor-Acceptor	:GLY147:O	:4b:O13
Interactions-6b	Distance Å	Bonding	Bonding Types	Binding site of enzyme	Binding site of ligand
:THR146:HN - :6b:O8	1.7104	Hydrogen Bond	Conventional Hydrogen Bond	:THR146:HN	:6b:O8
:6b:H25 - :LYS156:O	1.9303	Hydrogen Bond	Conventional Hydrogen Bond	:LYS156:O	:6b:H25
:GLY145:HA2 - :6b:O8	2.8622	Hydrogen Bond	Carbon Hydrogen Bond	:GLY145:HA2	:6b:O8
:GLY147:HA2 - :6b:O12	2.8655	Hydrogen Bond	Carbon Hydrogen Bond	:GLY147:HA2	:6b:O12
:ASN148:HA - :6b:O13	2.2940	Hydrogen Bond	Carbon Hydrogen Bond	:ASN148:HA	:6b:O13
:THR146:HN - :6b	2.2290	Hydrogen Bond	Pi-Donor Hydrogen Bond	:THR146:HN	:6b
:LYS156:HN - :6b	3.2257	Hydrogen Bond	Pi-Donor Hydrogen Bond	:LYS156:HN	:6b
:SER158:HN - :6b	2.6759	Hydrogen Bond	Pi-Donor Hydrogen Bond	:SER158:HN	:6b
:THR146:HB - :6b	2.8548	Hydrophobic	Pi-Sigma	:THR146:HB	:6b
:LYS156:O - :6b	2.8449	Other	Pi-Lone Pair	:LYS156:O	:6b
:6b:BR22 - :PRO157	5.4976	Hydrophobic	Alkyl	:PRO157	:6b:BR22
:6b:BR22 - :LEU160	4.4705	Hydrophobic	Alkyl	:LEU160	:6b:BR22
:6b:BR22 - :LEU165	3.5148	Hydrophobic	Alkyl	:LEU165	:6b:BR22
:6b - :LYS156	5.2862	Hydrophobic	Pi-Alkyl	:LYS156	:6b

:6b - :LYS156	4.7418	Hydrophobic	Pi-Alkyl	:LYS156	:6b
:6b - :PRO157	5.3195	Hydrophobic	Pi-Alkyl	:PRO157	:6b
:6b - :LEU165	4.7374	Hydrophobic	Pi-Alkyl	:LEU165	:6b
Interactions-6a	Distance Å	Bonding	Bonding Types	Binding site of enzyme	Binding site of ligand
:6a:H26 - :THR146:O	1.8451	Hydrogen Bond	Conventional Hydrogen Bond	:THR146:O	:6a:H26
:PRO157:HA - :6a:O13	2.6298	Hydrogen Bond	Carbon Hydrogen Bond	:PRO157:HA	:6a:O13
:6a:H6 - :THR146:O	2.8603	Hydrogen Bond	Carbon Hydrogen Bond	:THR146:O	:6a:H6
:LYS156:HN - :6a	2.5954	Hydrogen Bond	Pi-Donor Hydrogen Bond	:LYS156:HN	:6a
:SER158:HN - :6a	3.3371	Hydrogen Bond	Pi-Donor Hydrogen Bond	:SER158:HN	:6a
:SER158:HN - :6a	2.1245	Hydrogen Bond	Pi-Donor Hydrogen Bond	:SER158:HN	:6a
:6a:CL10 - :LEU160	4.2374	Hydrophobic	Alkyl	:LEU160	:6a:CL10
:6a:CL10 - :LEU165	5.3035	Hydrophobic	Alkyl	:LEU165	:6a:CL10
:TYR155 - :6a:BR23	4.6546	Hydrophobic	Pi-Alkyl	:TYR155	:6a:BR23
:6a - :LEU165	5.1612	Hydrophobic	Pi-Alkyl	:LEU165	:6a
:6a - :PRO157	5.0896	Hydrophobic	Pi-Alkyl	:PRO157	:6a
:6a - :LEU165	4.2515	Hydrophobic	Pi-Alkyl	:LEU165	:6a
:6a - :LYS156	5.0985	Hydrophobic	Pi-Alkyl	:LYS156	:6a
Interactions-7a	Distance Å	Bonding	Bonding Types	Binding site of enzyme	Binding site of ligand
:THR149:HN - :7a:O13	3.0648	Hydrogen Bond	Conventional Hydrogen Bond	:THR149:HN	:7a:O13
:LYS156:HN - :7a:O12	1.9569	Hydrogen Bond	Conventional Hydrogen Bond	:LYS156:HN	:7a:O12
:7a:H26 - :THR146:O	2.0151	Hydrogen Bond	Conventional Hydrogen Bond	:THR146:O	:7a:H26
:7a:H4 - :THR146:O	2.2830	Hydrogen Bond	Conventional Hydrogen Bond	:THR146:O	:7a:H4
:ASN148:HA - :7a:N14	2.7363	Hydrogen Bond	Carbon Hydrogen Bond	:ASN148:HA	:7a:N14
:TYR155:HA - :7a:O12	2.6489	Hydrogen Bond	Carbon Hydrogen Bond	:TYR155:HA	:7a:O12
:SER158:HB1 - :7a:O8	2.7891	Hydrogen Bond	Carbon Hydrogen Bond	:SER158:HB1	:7a:O8
:7a:H6 - :LYS156:O	2.4835	Hydrogen Bond	Carbon Hydrogen Bond	:LYS156:O	:7a:H6
:THR146:HN - :7a	2.1029	Hydrogen Bond	Pi-Donor Hydrogen Bond	:THR146:HN	:7a

:PRO157:HA - :7a	2.2650	Hydrophobic	Pi-Sigma	:PRO157:HA	:7a
:7a:S11 - :TYR155	5.8584	Other	Pi-Sulfur	:TYR155	:7a:S11
:LYS156:O - :7a	2.9959	Other	Pi-Lone Pair	:LYS156:O	:7a
:7a:CL10 - :LYS156	4.1006	Hydrophobic	Alkyl	:LYS156	:7a:CL10
:7a:C23 - :PRO157	5.1711	Hydrophobic	Alkyl	:PRO157	:7a:C23
:7a:C23 - :LEU165	3.6029	Hydrophobic	Alkyl	:LEU165	:7a:C23
:7a - :LYS156	3.7359	Hydrophobic	Pi-Alkyl	:LYS156	:7a
:7a - :LYS156	4.3841	Hydrophobic	Pi-Alkyl	:LYS156	:7a
:GLY147:O - :7a:O13	2.6019	Unfavorable	Unfavorable Acceptor-Acceptor	:GLY147:O	:7a:O13

Table S4. The Lipinski and Veber rules analysis of four compounds.

Name	AlogP	MW	Num_H_Acceptors_Lipinski (≤ 10) (≤ 5)	Num_H_Donors_Lipinski (≤ 5)	MPSA ($\leq 140 \text{ A}^2$)	NRB (≤ 10)	Num_H_Acceptors (≤ 12)	Num_H_Donors (≤ 12)
	(≤ 5)	($\leq 500 \text{ g/mol}$)						
4b	3.6	372.226	6	1	93.47	4	4	1
6b	3.684	416.677	6	1	93.47	4	4	1
6a	3.684	416.677	6	1	93.47	4	4	1
7a	3.422	351.808	6	1	93.47	4	4	1

Footnote: Comp, compound; ALogP, octanol/water partition coefficient, a measure for lipophilicity; MW, molecular weight; MPSA, molecular polar surface area; Num_H_Acceptors_Lipinski, Number of hydrogen bond acceptors; Num_H_Donors_Lipinski, Number of hydrogen bond donors; NRB, Number of Rotatable bonds; Num_H_Acceptors, Number of hydrogen bond acceptors based on Veber; Num_H_Donors, Number of hydrogen bond donors based on Veber.

Table S5. ADMET analysis of four compounds.

Name	PSA_2D(< 140 Å ²)	AlogP98(< 5)	Solubility	HIA	BBB level	Hepatotoxic	CYP2D6	PPB
4b	82.488	3.600	2	0	2	TRUE	FALSE	TRUE
6b	82.488	3.684	2	0	2	TRUE	FALSE	TRUE
6a	82.488	3.684	2	0	2	TRUE	FALSE	TRUE
7a	82.488	3.422	2	0	2	TRUE	FALSE	TRUE

Abbreviations: PSA, polar surface area; AlogP98, the logarithm of the partition coefficient between n-octanol and water; BBB blood brain barrier; CYP2D6 cytochrome P450 2D6 binding; PPB plasma protein binding, more than 90% for PPB: Chemicals strongly bound. Less than 90% for PPB: Chemicals weakly bound.

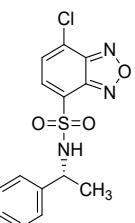
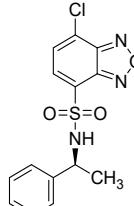
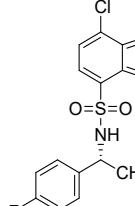
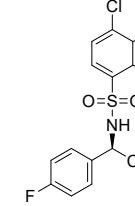
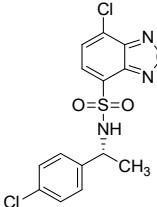
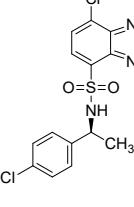
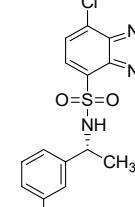
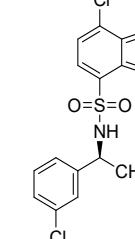
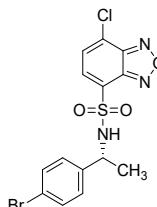
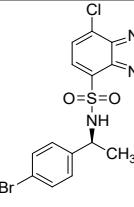
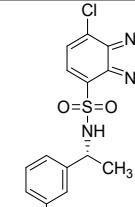
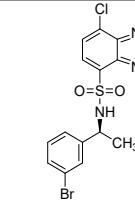
Table S6. Binding energy values of **6a** compound with HIF-1Beta, AKT1 and PI3K, respectively.

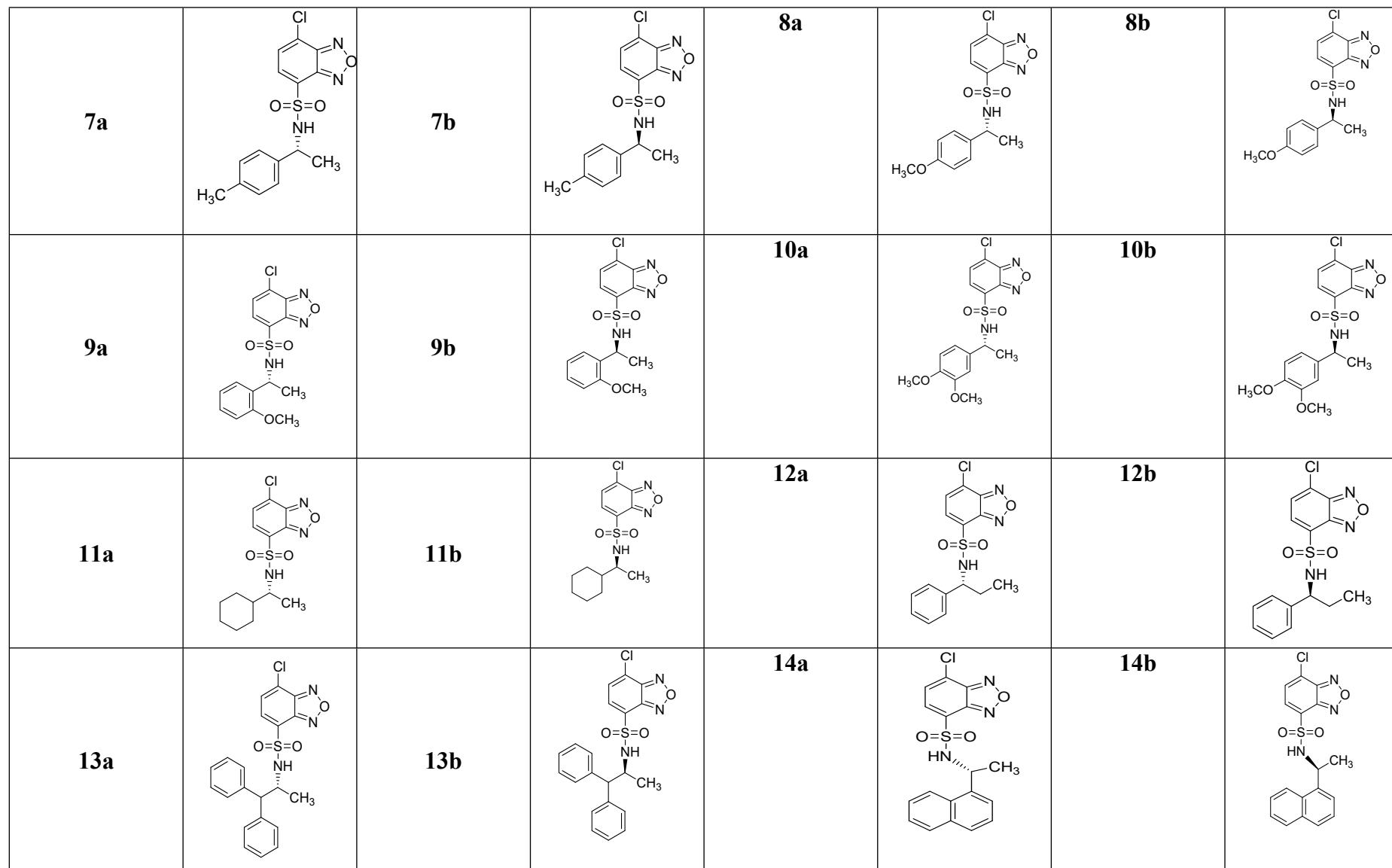
Ligand Name-AutoDock Vina	Binding Energy (kcal/mol)
6R-HIF-1Beta	-8.94
6R-AKT1	-6.90
6R-PI3K	-8.00

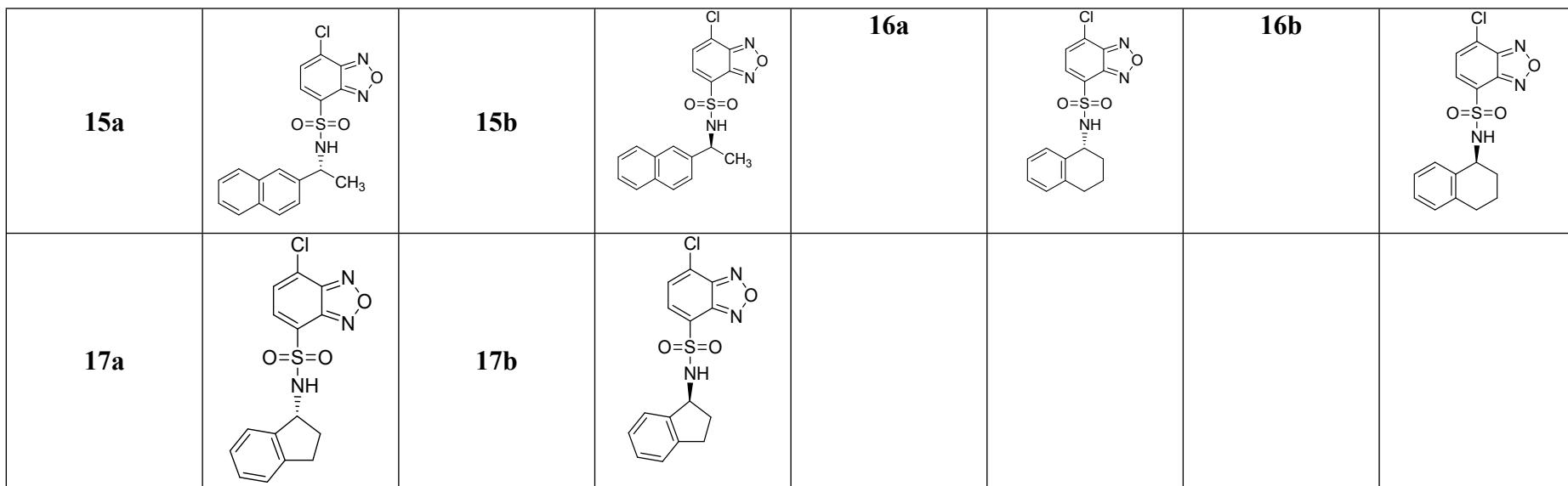
Table S7. Interaction detail data of 6a compound against AKT1 and PI3K, respectively.

Interactions-6a-AKT1	Distance Å	Bonding	Bonding Types	Binding site of enzyme	Binding site of ligand
F:THR6:HN - 6a:O8	1.87727	Hydrogen Bond	Conventional Hydrogen Bond	F:THR6:HN	6a:O8
F:THR6:HB - 6a:O13	2.88046	Hydrogen Bond	Carbon Hydrogen Bond	F:THR6:HB	6a:O13
6a:S11 - A:HIS354	5.71343	Other	Pi-Sulfur	A:HIS354	6a:S11
F:PHE8 - 6a:	3.9131	Hydrophobic	Pi-Pi Stacked	F:PHE8	6a:
A:HIS354 - 6a:	4.56936	Hydrophobic	Pi-Pi T-shaped	A:HIS354	6a:
A:HIS354 - 6a:	4.9717	Hydrophobic	Pi-Pi T-shaped	A:HIS354	6a:
A:HIS354 - 6a:Cl22	5.41794	Hydrophobic	Pi-Alkyl	A:HIS354	6a:Cl22
F:PHE8 - 6a:Br11	4.63796	Hydrophobic	Pi-Alkyl	F:PHE8	6a:Br11
6a: - A:PRO313	5.40773	Hydrophobic	Pi-Alkyl	A:PRO313	6a:
6a: - A:PRO313	4.70685	Hydrophobic	Pi-Alkyl	A:PRO313	6a:
Interactions-6a-PI3K	Distance Å	Bonding	Bonding Types	Binding site of enzyme	Binding site of ligand
A:LYS298:HZ3 - 6a:O8	2.7053	Hydrogen Bond	Conventional Hydrogen Bond	A:LYS298:HZ3	6a:O8
6a:H2 - A:GLN291:OE1	2.25549	Hydrogen Bond	Carbon Hydrogen Bond	A:GLN291:OE1	6a:H2
A:GLU852:OE1 - 6a:	4.24625	Electrostatic	Pi-Anion	A:GLU852:OE1	6a:
A:GLU852:OE1 - 6a:	3.5157	Electrostatic	Pi-Anion	A:GLU852:OE1	6a:
6a:S11 - A:HIS658	5.78568	Other	Pi-Sulfur	A:HIS658	6a:S11
6a:Br11 - A:PRO208	4.40224	Hydrophobic	Alkyl	A:PRO208	6a:Br11
6a:Br11 - A:LEU211	5.07362	Hydrophobic	Alkyl	A:LEU211	6a:Br11
6a:Br11 - A:ARG294	3.95752	Hydrophobic	Alkyl	A:ARG294	6a:Br11
A:TYR210 - 6a:CL10	5.18303	Hydrophobic	Pi-Alkyl	A:TYR210	6a:CL10
6a: - A:ARG294	4.79903	Hydrophobic	Pi-Alkyl	A:ARG294	6a:
6a: - A:LYS298	4.82192	Hydrophobic	Pi-Alkyl	A:LYS298	6a:
6a: - A:LYS298	5.18851	Hydrophobic	Pi-Alkyl	A:LYS298	6a:

CHEMISTRY

Compound number	Formula	Compound number	Formula	Compound number	Formula	Compound number	Formula
1a		1b		2a		2b	
3a		3b		4a		4b	
5a		5b		6a		6b	



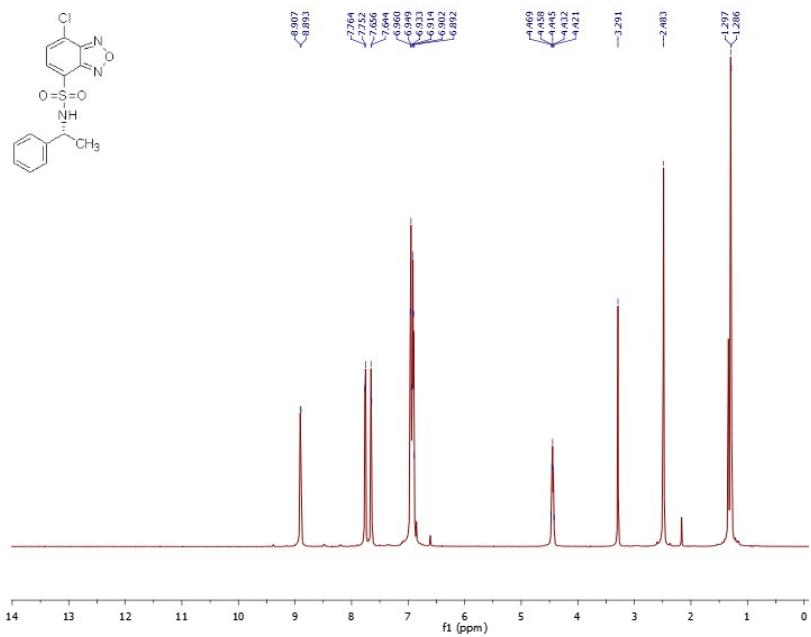
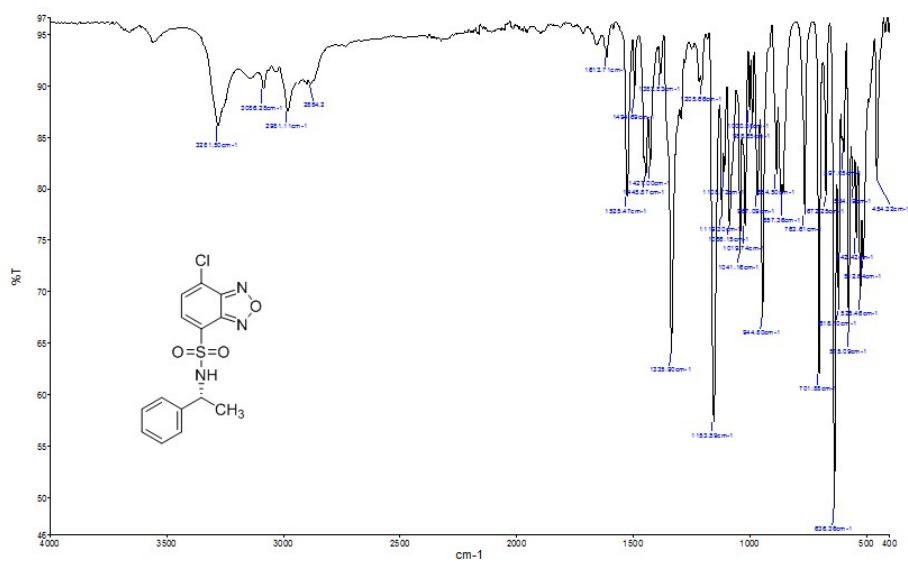


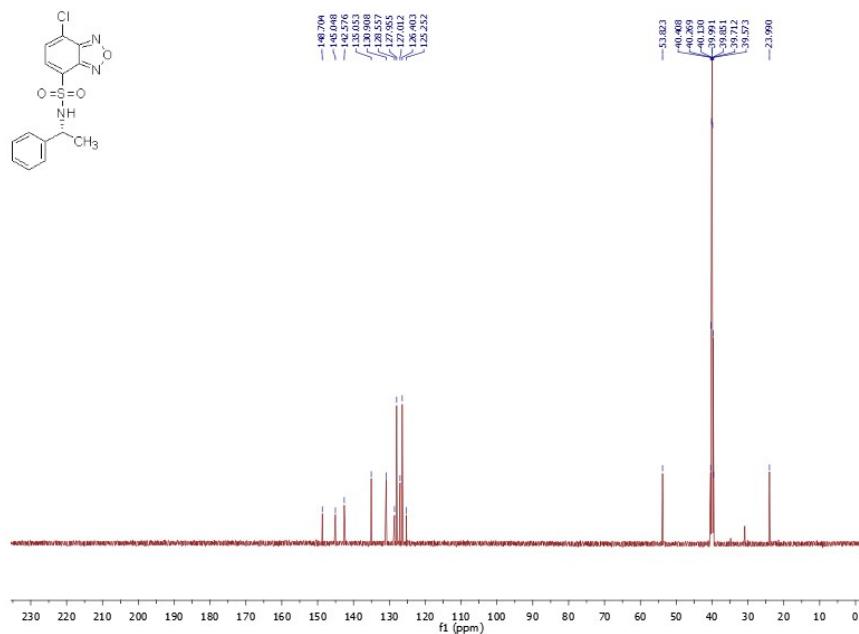
Scheme S. The chemical structures of compounds **1a-17a** and **1b-17b**

Example SMILES Document

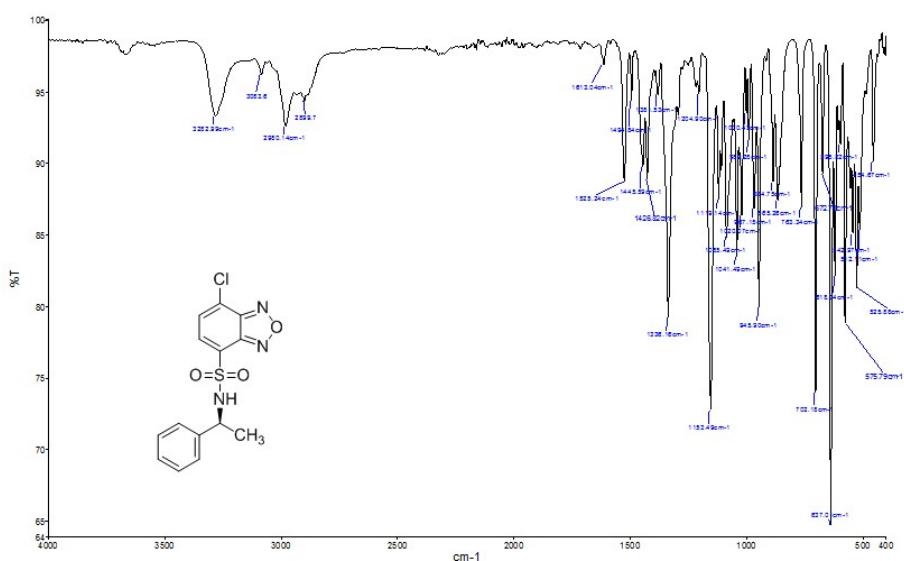
Compound	Smiles
1a	C[C@@H](NS(=O)(=O)c1ccc(Cl)c2nonc12)c1ccccc1
2a	Fc1ccc(cc1)[C@@H](C)NS(=O)(=O)c1ccc(Cl)c2nonc12
3a	Clc1ccc(cc1)[C@@H](C)NS(=O)(=O)c1ccc(Cl)c2nonc12
4a	Clc1cccc(c1)[C@@H](C)NS(=O)(=O)c1ccc(Cl)c2nonc12
5a	Brc1ccc(cc1)[C@@H](C)NS(=O)(=O)c1ccc(Cl)c2nonc12
6a	Brc1cccc(c1)[C@@H](C)NS(=O)(=O)c1ccc(Cl)c2nonc12
7a	Cc1ccc(cc1)[C@@H](C)NS(=O)(=O)c1ccc(Cl)c2nonc12
8a	COc1ccc(cc1)[C@@H](C)NS(=O)(=O)c1ccc(Cl)c2nonc12
9a	COc1ccccc1[C@@H](C)NS(=O)(=O)c1ccc(Cl)c2nonc12
10a	COc1ccc(cc1OC)[C@@H](C)NS(=O)(=O)c1ccc(Cl)c2nonc12
11a	C[C@@H](NS(=O)(=O)c1ccc(Cl)c2nonc12)C1CCCCC1
12a	CC[C@@H](NS(=O)(=O)c1ccc(Cl)c2nonc12)c1ccccc1
13a	C[C@@H](NS(=O)(=O)c1ccc(Cl)c2nonc12)C(c1ccccc1)c1ccccc1
14a	C[C@@H](NS(=O)(=O)c1ccc(Cl)c2nonc12)c1ccccc2ccccc21
15a	C[C@@H](NS(=O)(=O)c1ccc(Cl)c2nonc12)c1cc2ccccc2cc1
16a	O=S(=O)(N[C@@H]1CCCCc2ccccc21)c1ccc(Cl)c2nonc12
17a	O=S(=O)(N[C@@H]1CCc2ccccc21)c1ccc(Cl)c2nonc12
1b	C[C@H](NS(=O)(=O)c1ccc(Cl)c2nonc12)c1ccccc1
2b	Fc1ccc(cc1)[C@H](C)NS(=O)(=O)c1ccc(Cl)c2nonc12
3b	Clc1ccc(cc1)[C@H](C)NS(=O)(=O)c1ccc(Cl)c2nonc12
4b	Clc1cccc(c1)[C@H](C)NS(=O)(=O)c1ccc(Cl)c2nonc12
5b	Brc1ccc(cc1)[C@H](C)NS(=O)(=O)c1ccc(Cl)c2nonc12
6b	Brc1cccc(c1)[C@H](C)NS(=O)(=O)c1ccc(Cl)c2nonc12
7b	Cc1ccc(cc1)[C@H](C)NS(=O)(=O)c1ccc(Cl)c2nonc12
8b	COc1ccc(cc1)[C@H](C)NS(=O)(=O)c1ccc(Cl)c2nonc12
9b	COc1ccccc1[C@H](C)NS(=O)(=O)c1ccc(Cl)c2nonc12
10b	COc1ccc(cc1OC)[C@H](C)NS(=O)(=O)c1ccc(Cl)c2nonc12
11b	C[C@H](NS(=O)(=O)c1ccc(Cl)c2nonc12)C1CCCCC1
12b	CC[C@H](NS(=O)(=O)c1ccc(Cl)c2nonc12)c1ccccc1
13b	C[C@H](NS(=O)(=O)c1ccc(Cl)c2nonc12)C(c1ccccc1)c1ccccc1
14b	C[C@H](NS(=O)(=O)c1ccc(Cl)c2nonc12)c1ccccc2ccccc21
15b	C[C@H](NS(=O)(=O)c1ccc(Cl)c2nonc12)c1cc2ccccc2cc1
16b	O=S(=O)(N[C@H]1CCCCc2ccccc21)c1ccc(Cl)c2nonc12
17b	O=S(=O)(N[C@H]1CCc2ccccc21)c1ccc(Cl)c2nonc12

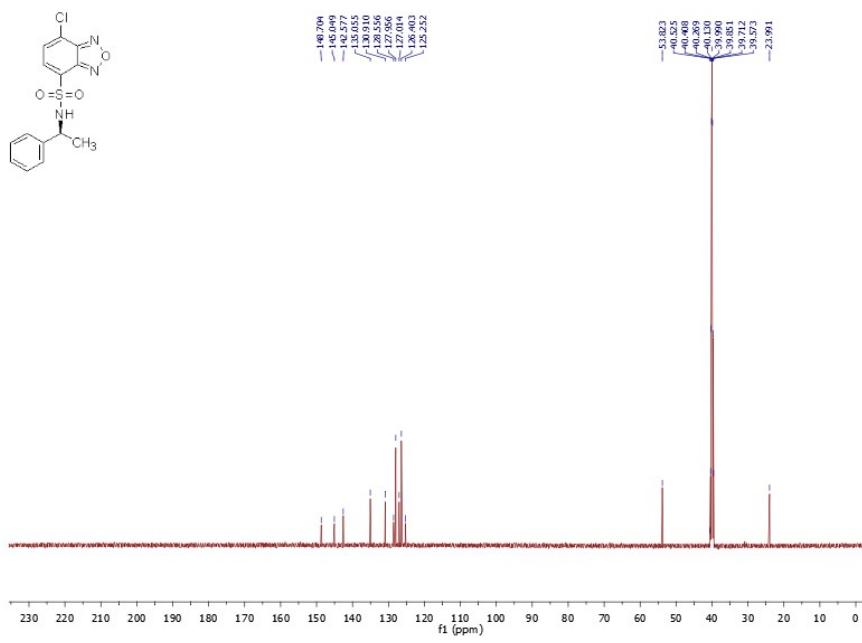
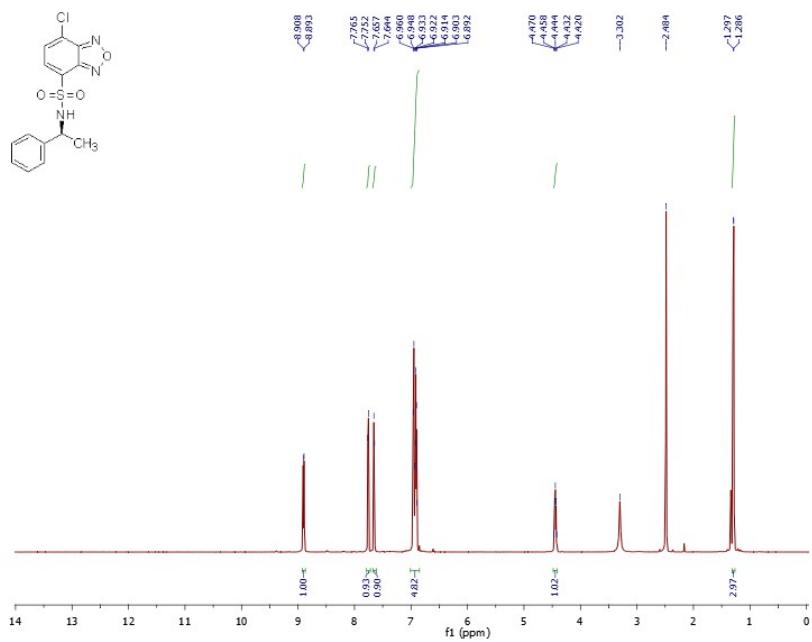
Compound 1a



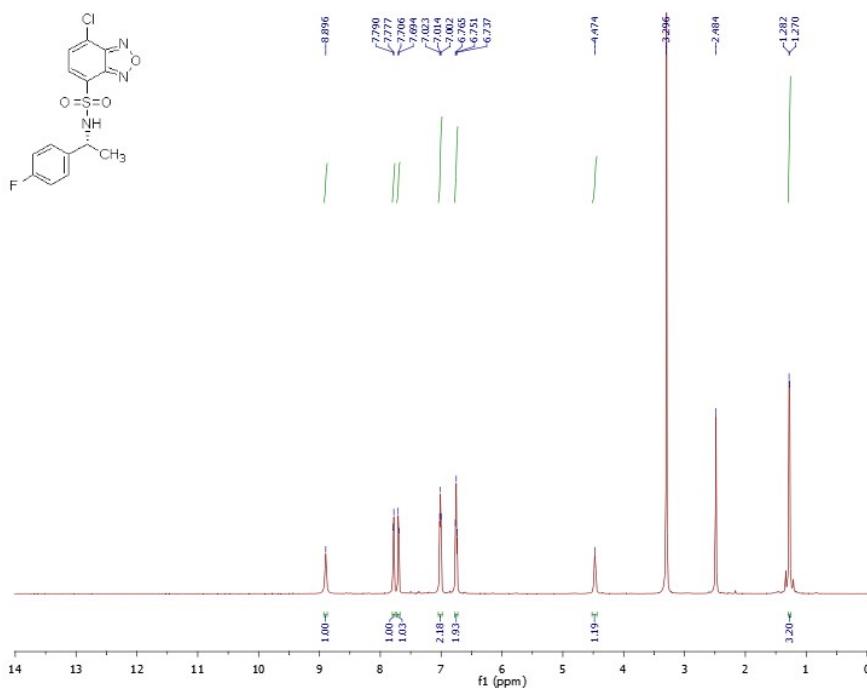
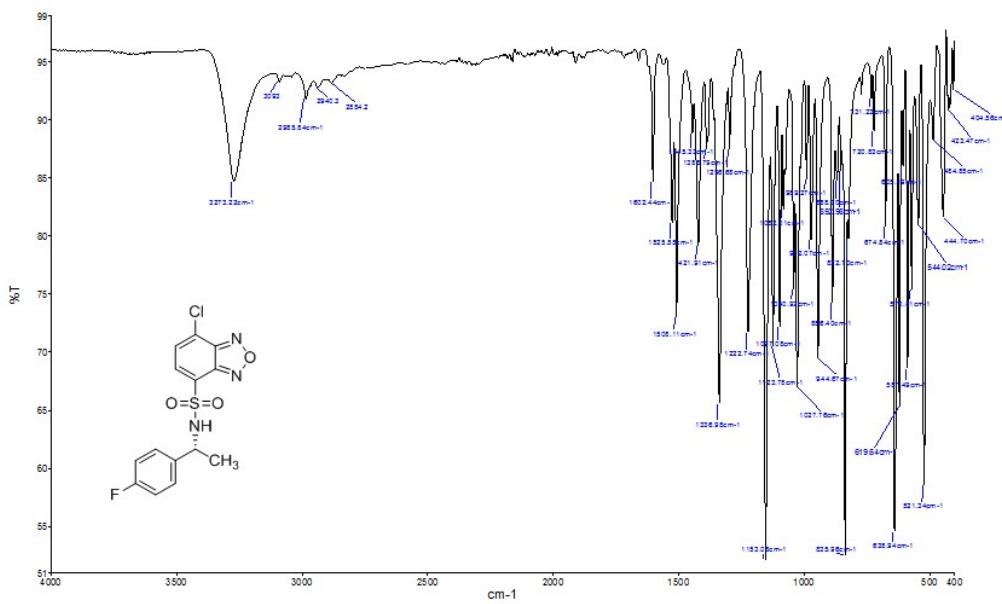


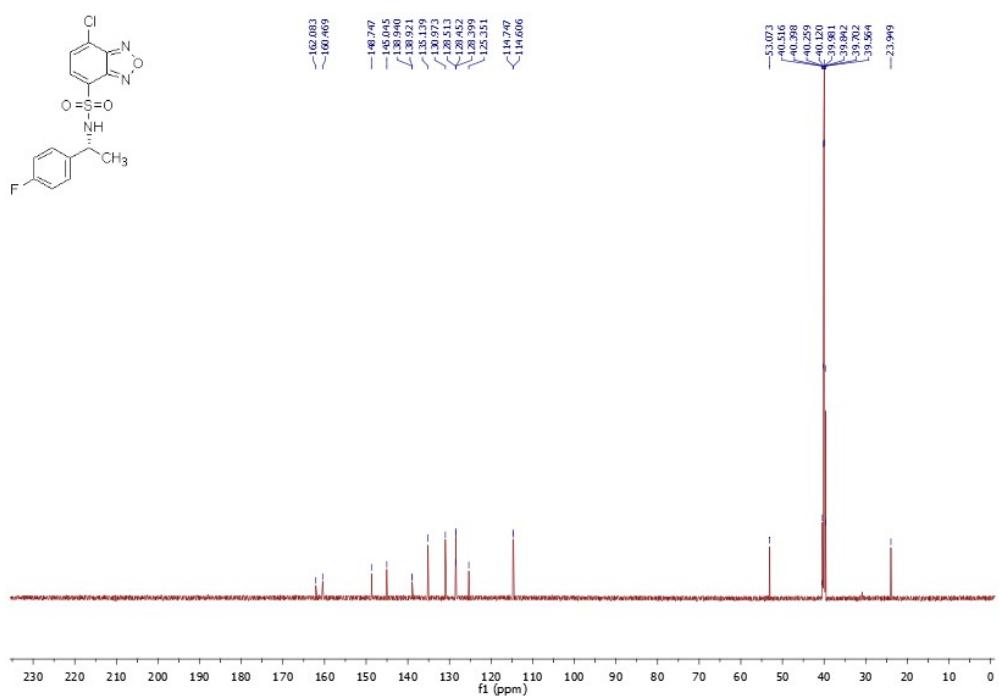
Compound 1b



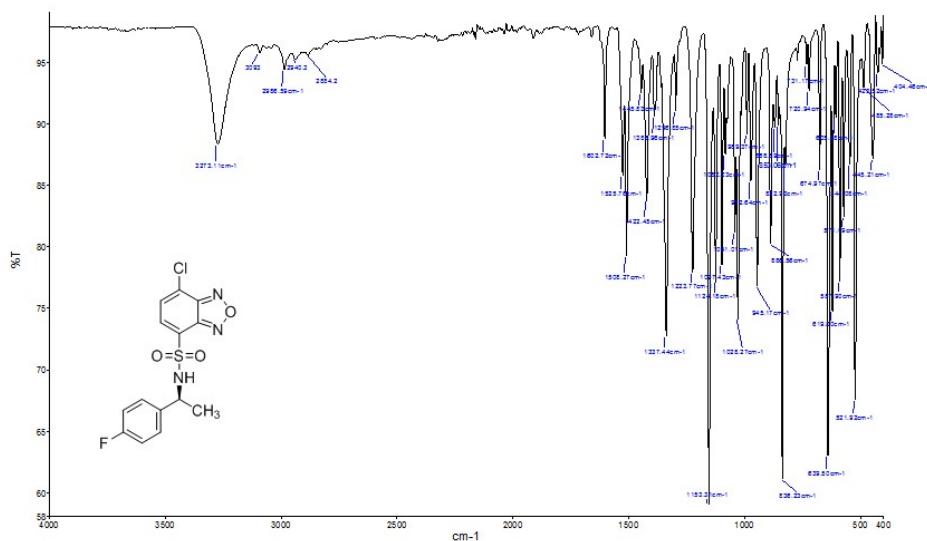


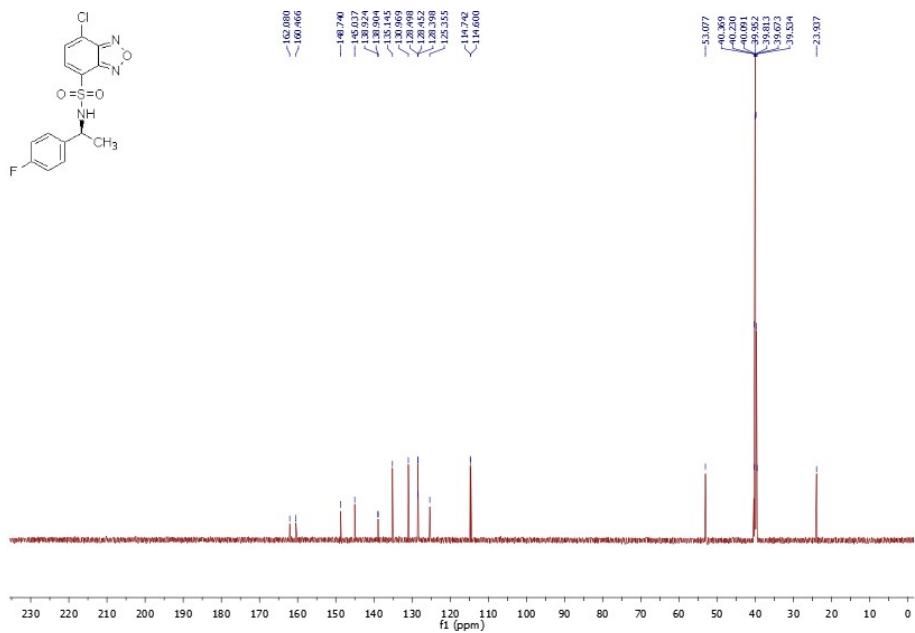
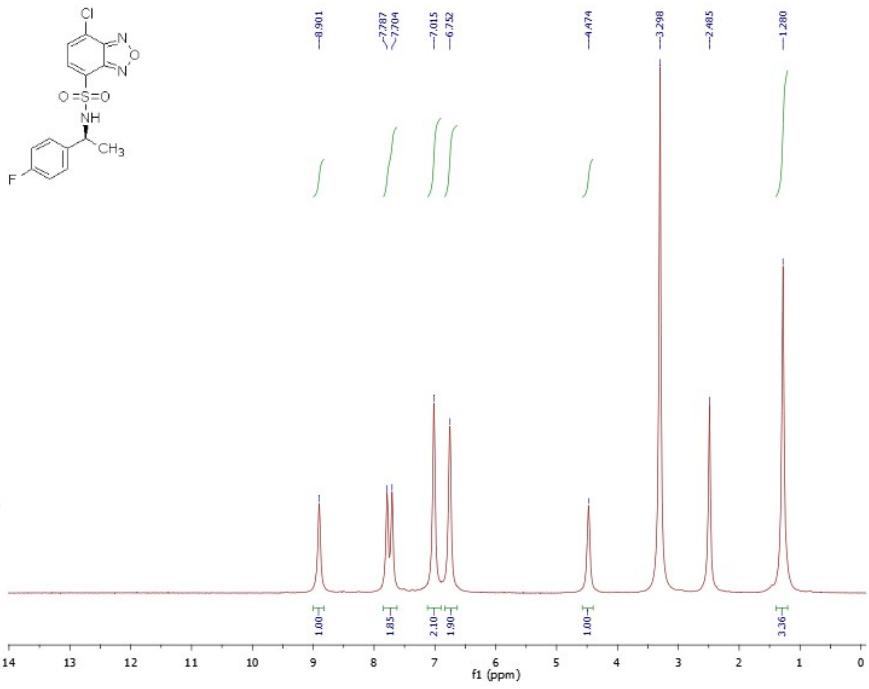
Compound 2a



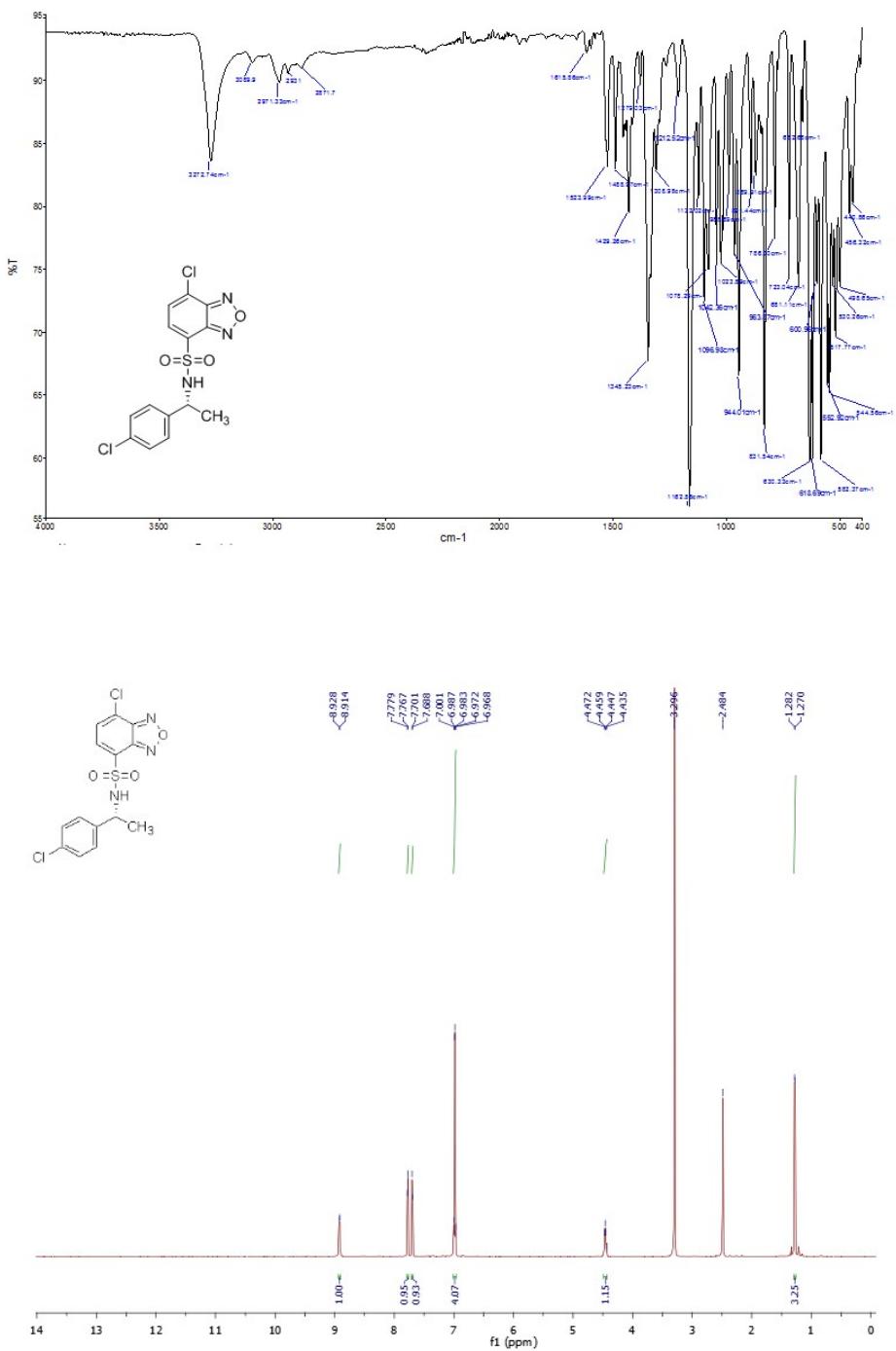


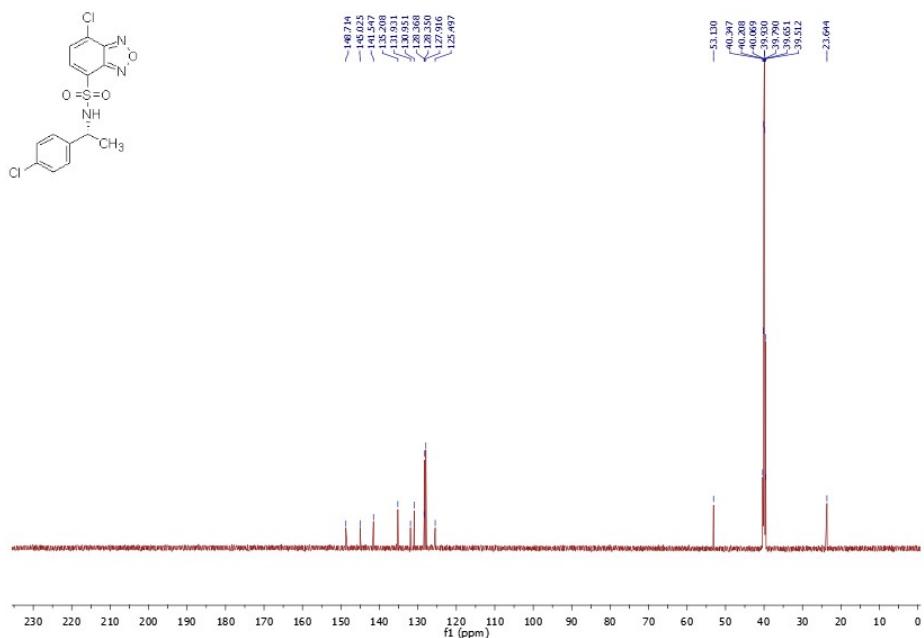
Compound 2b



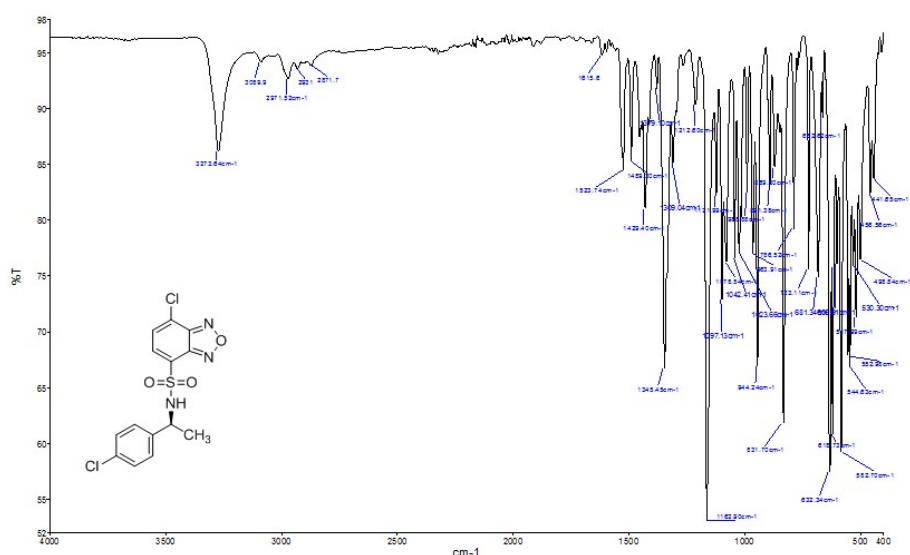


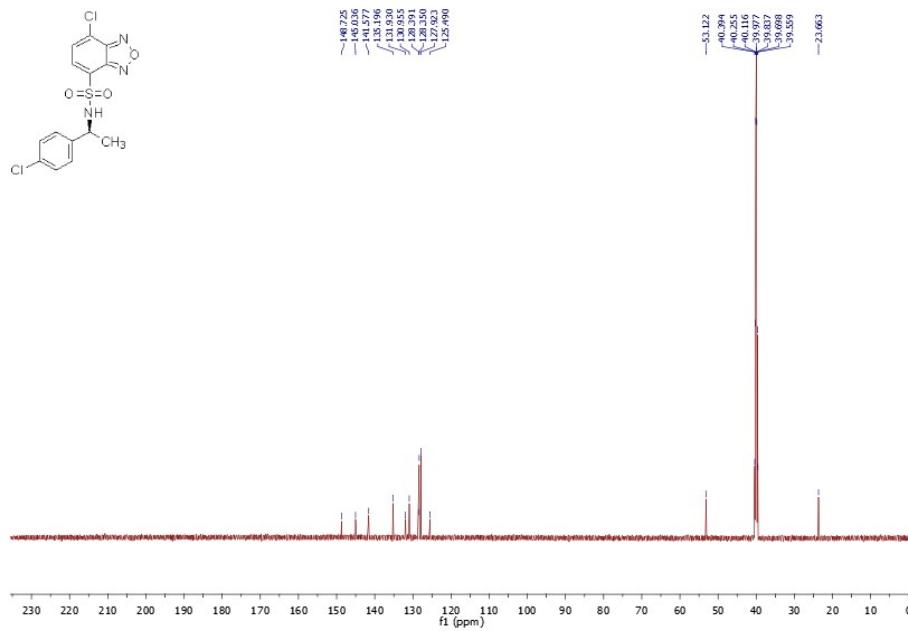
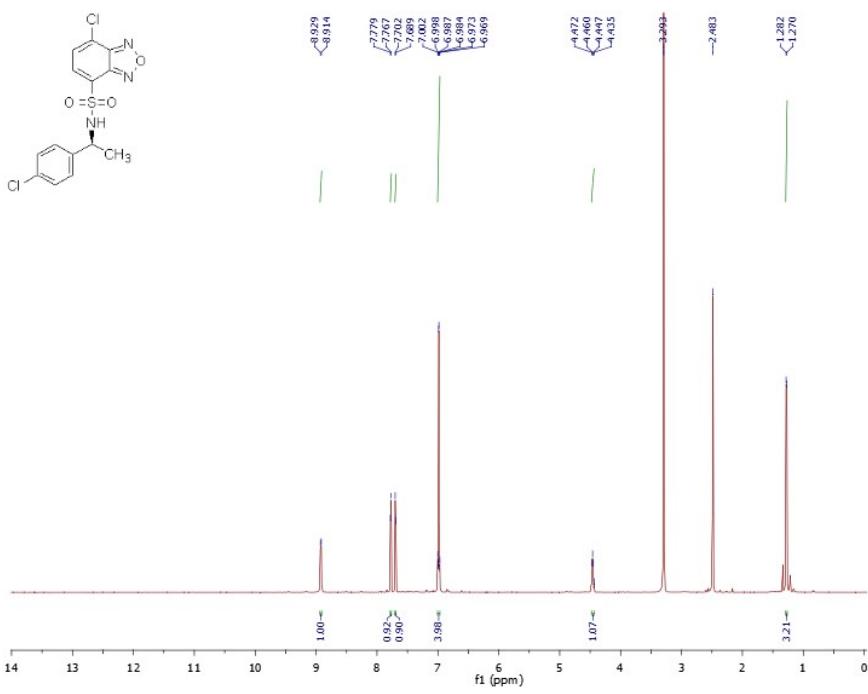
Compound 3a



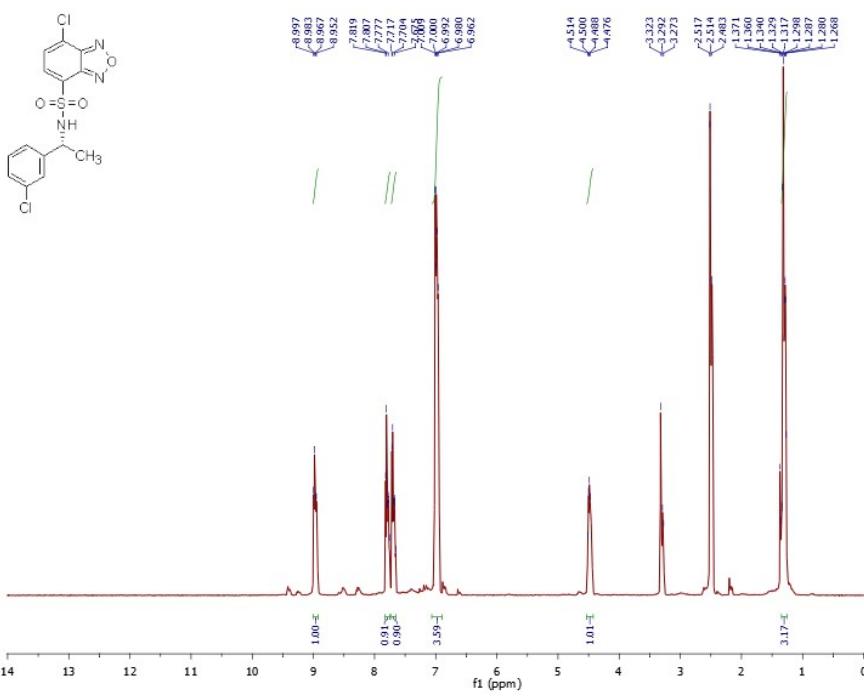
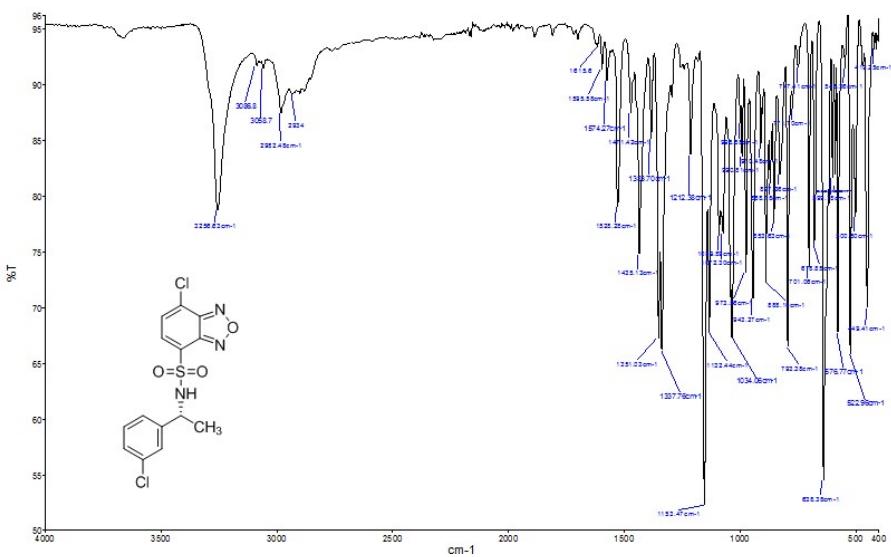


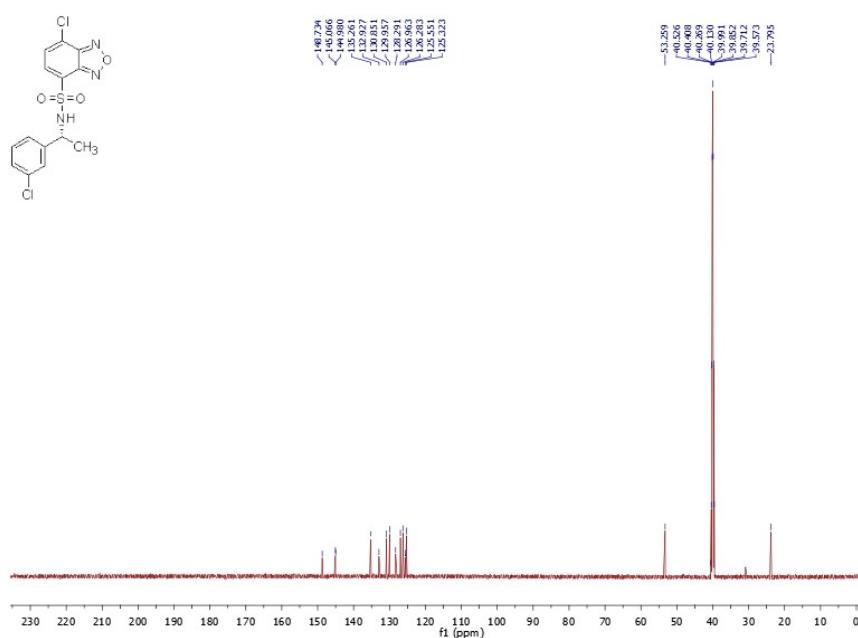
Compound 3b



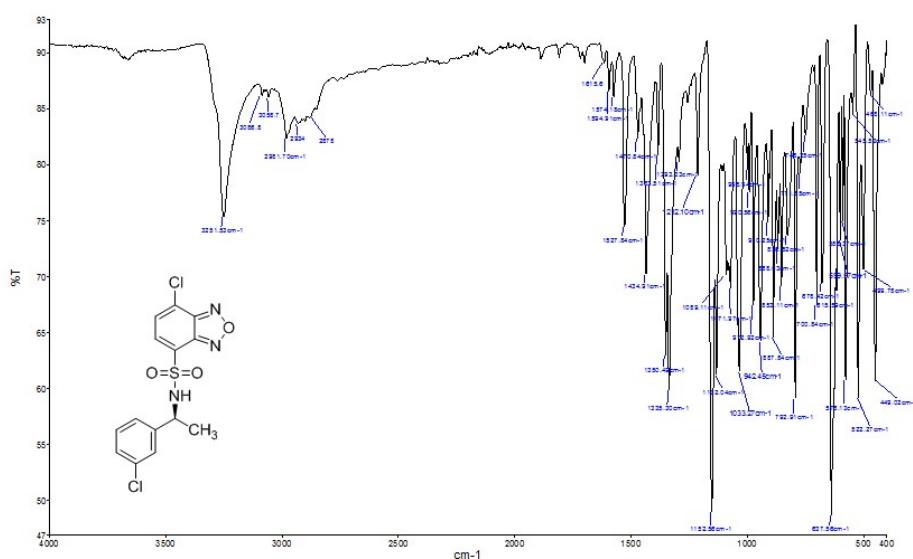


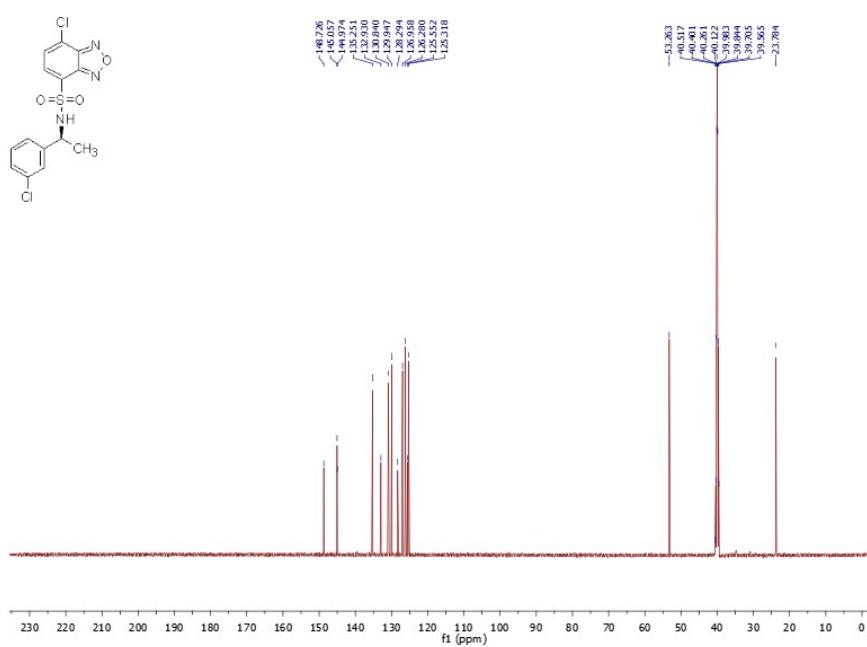
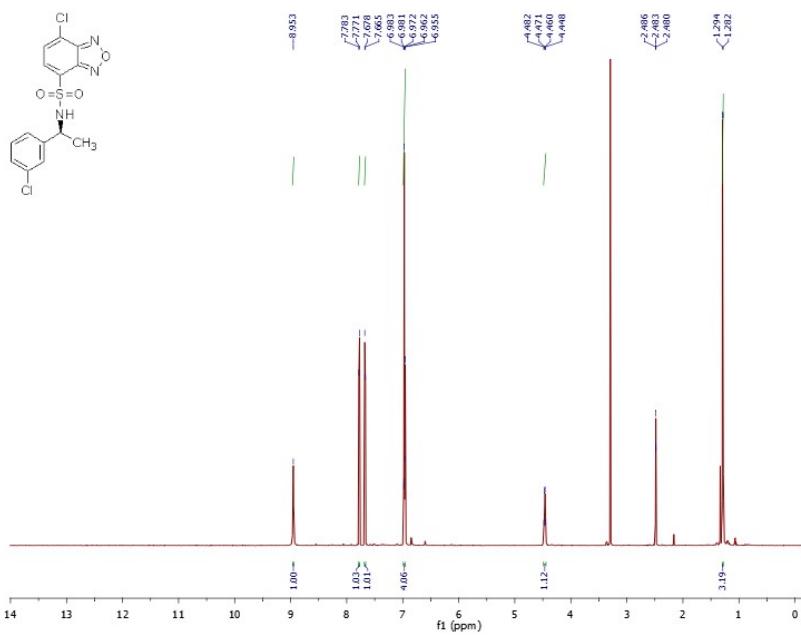
Compound 4a



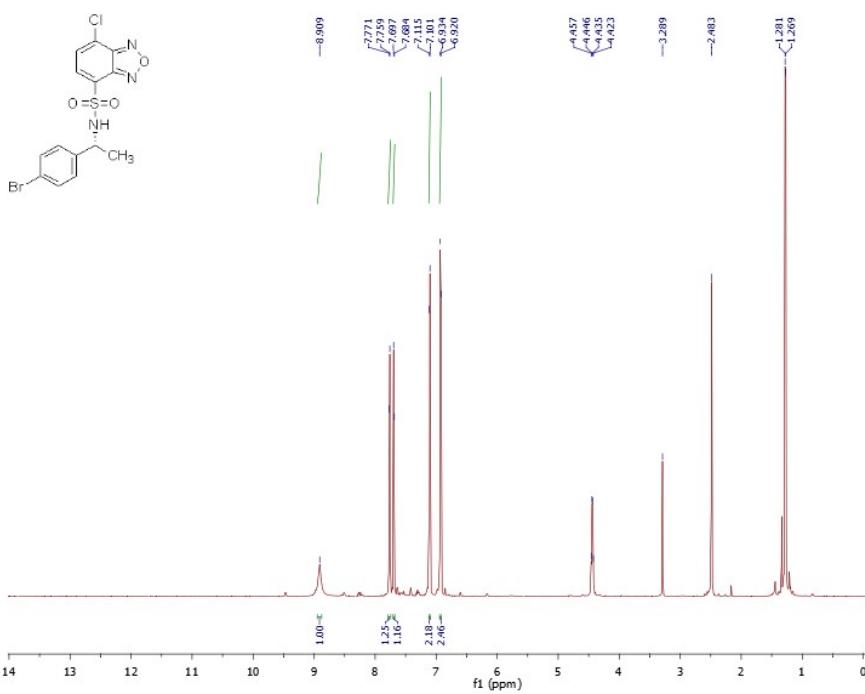
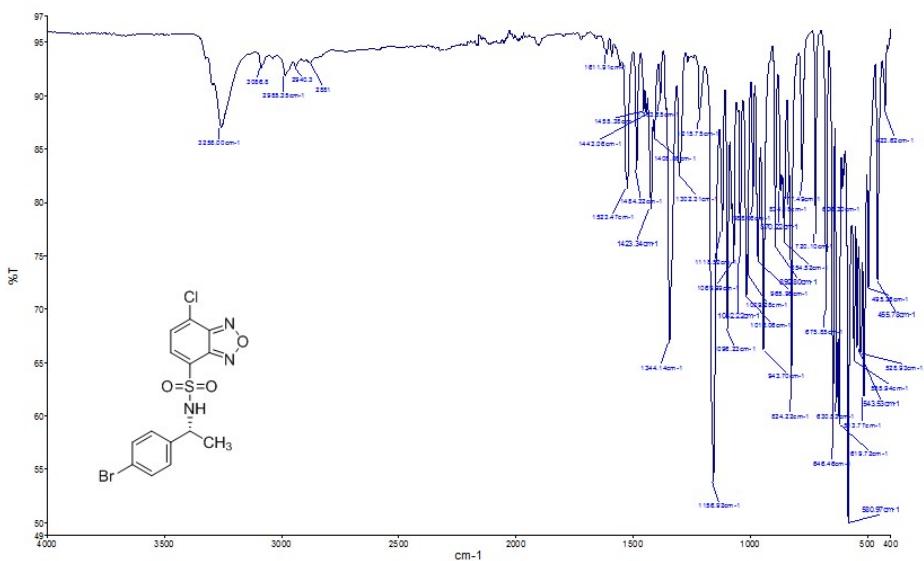


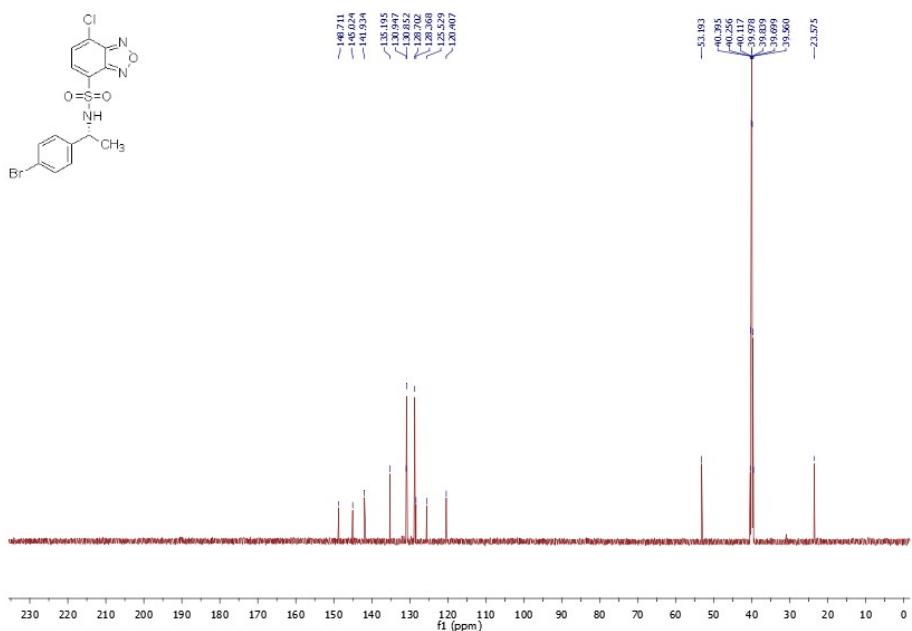
Compound 4b



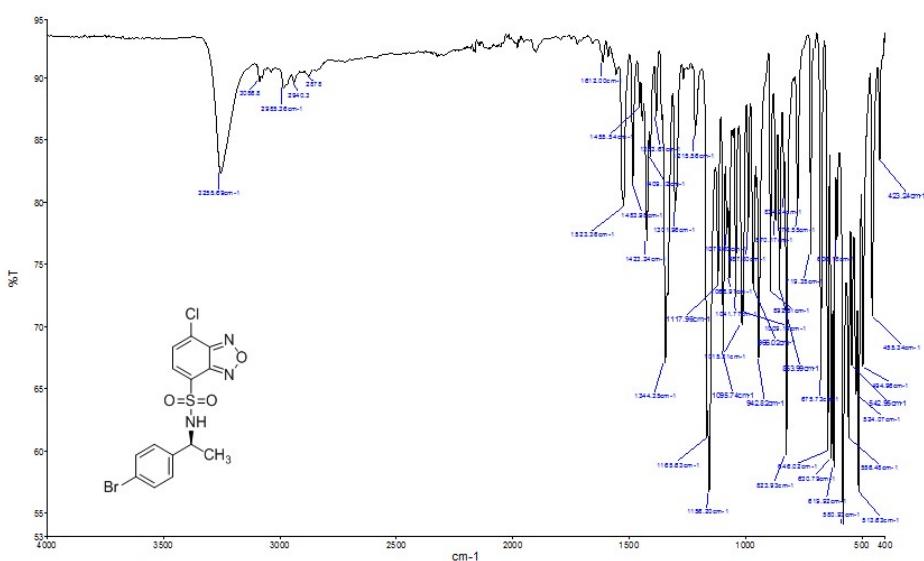


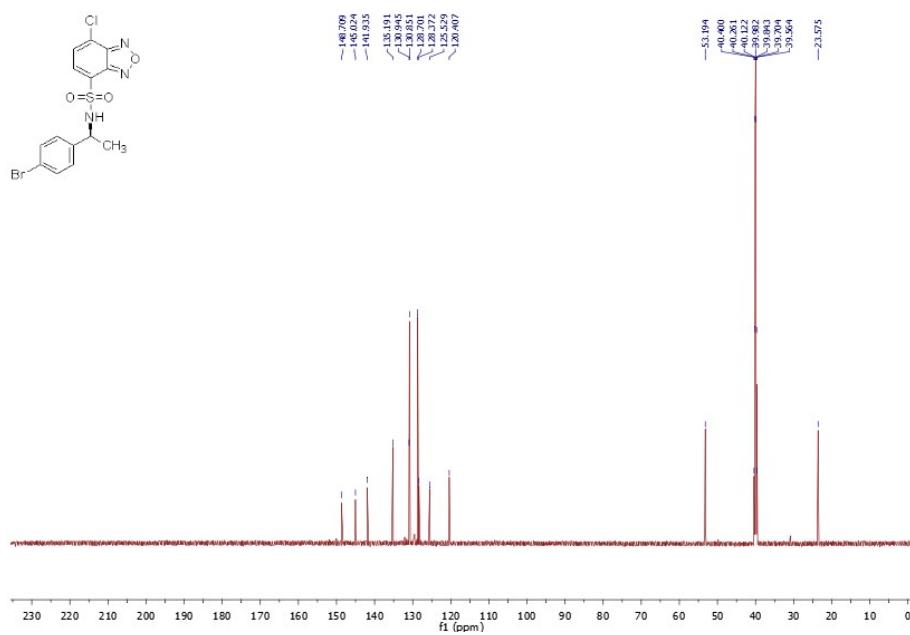
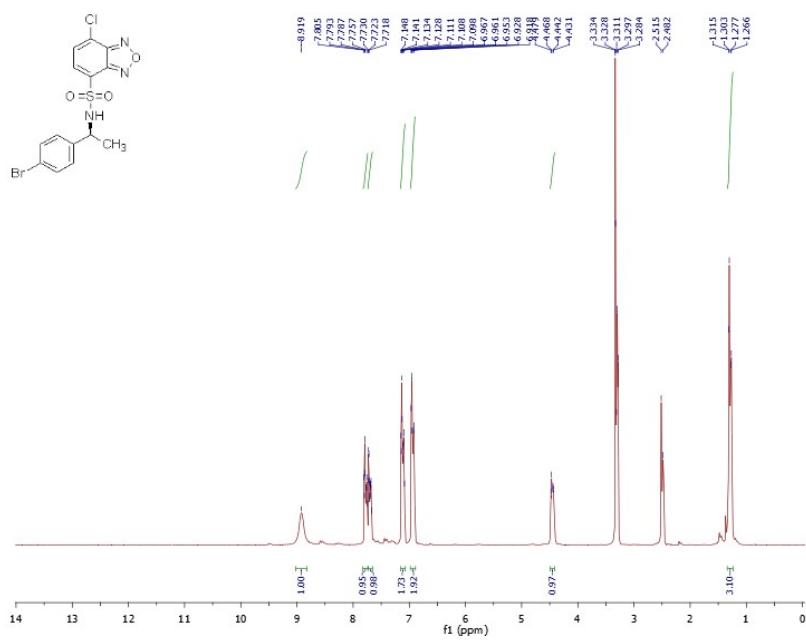
Compound 5a



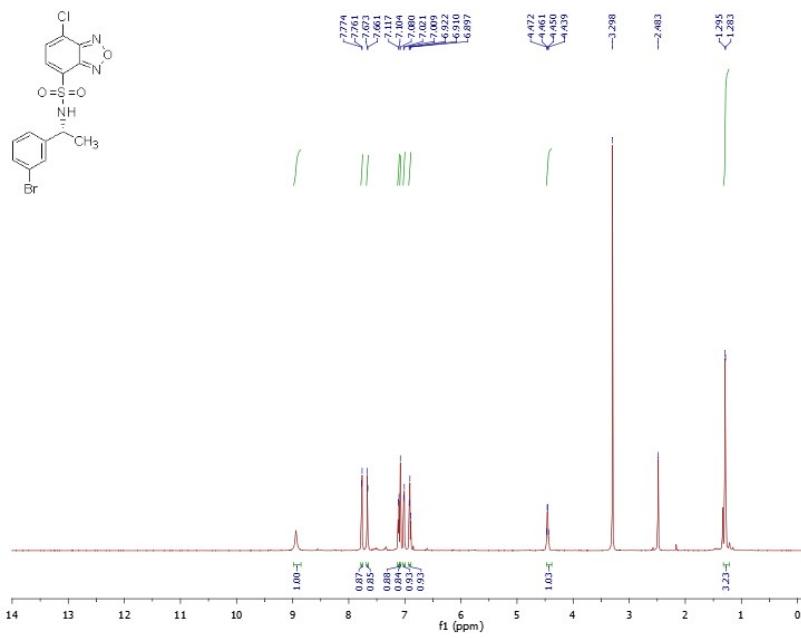
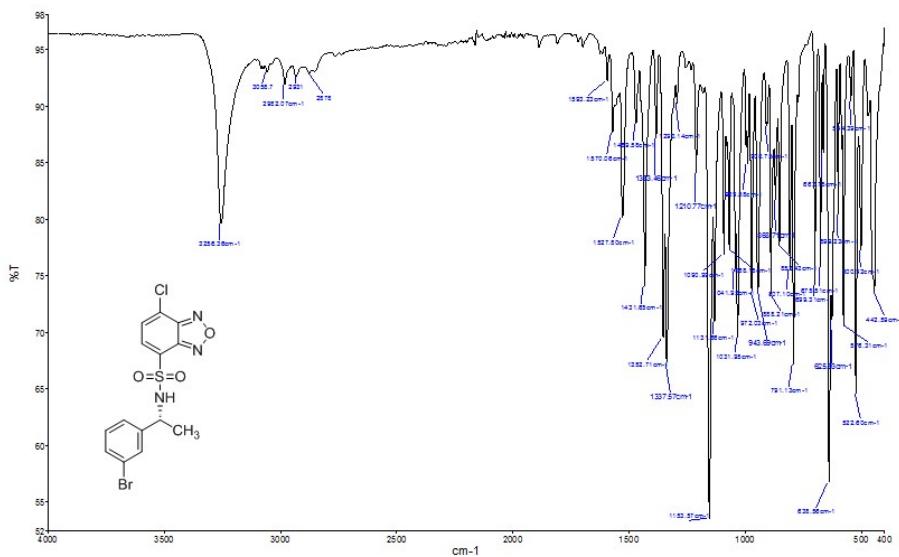


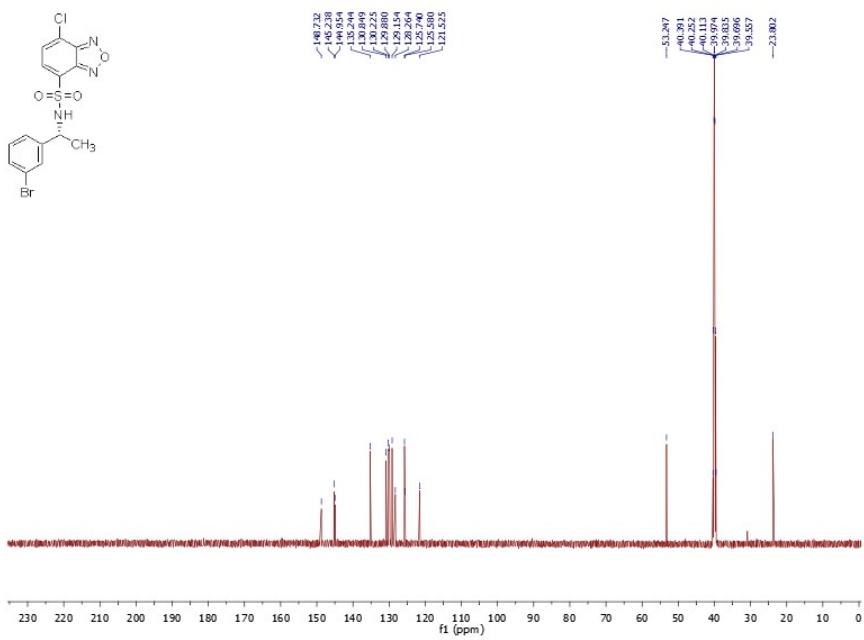
Compound 5b



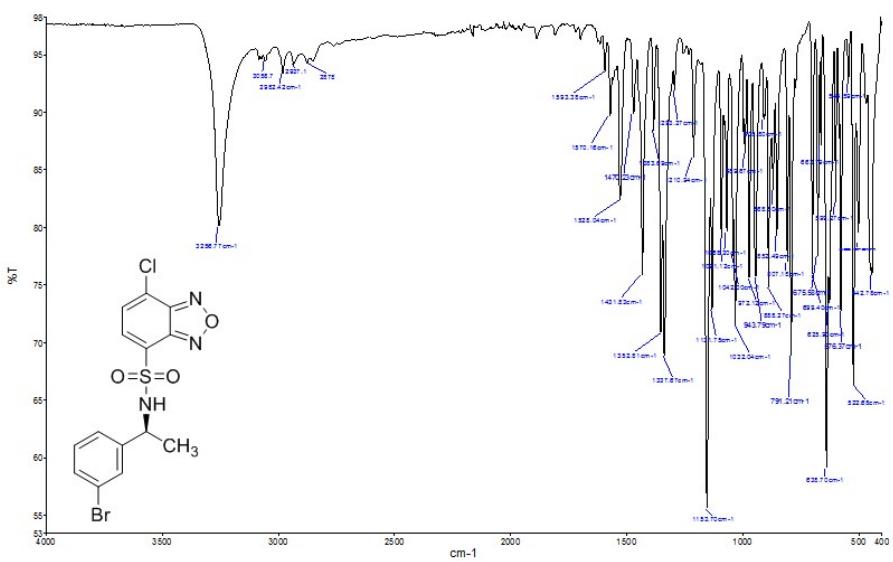


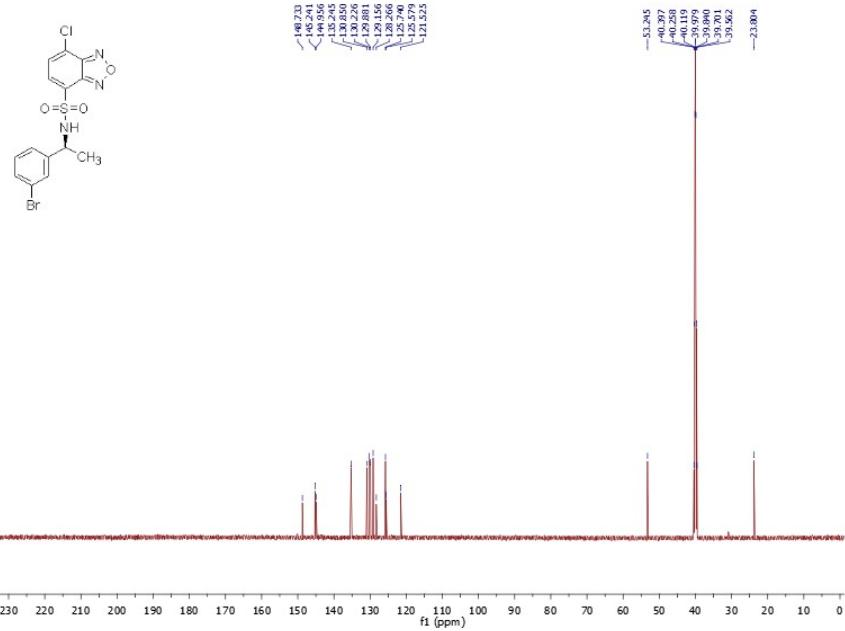
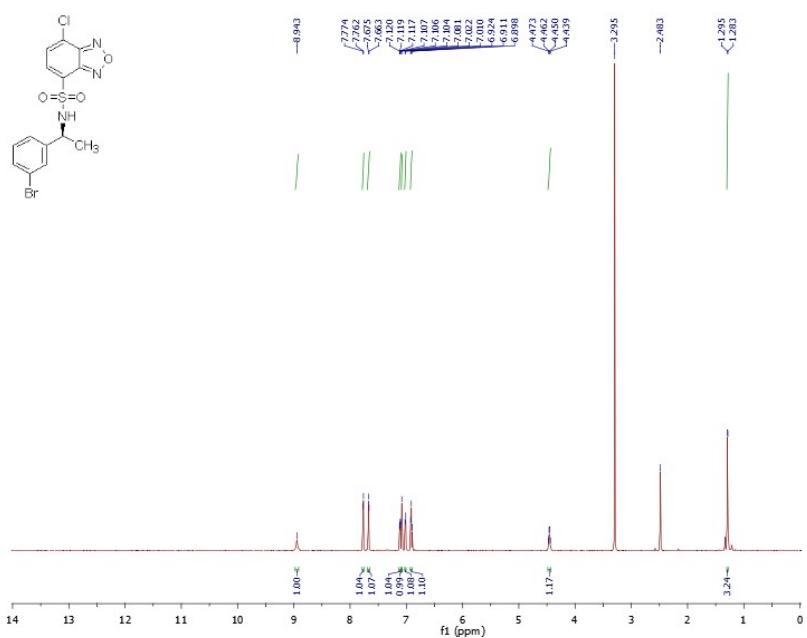
Compound 6a



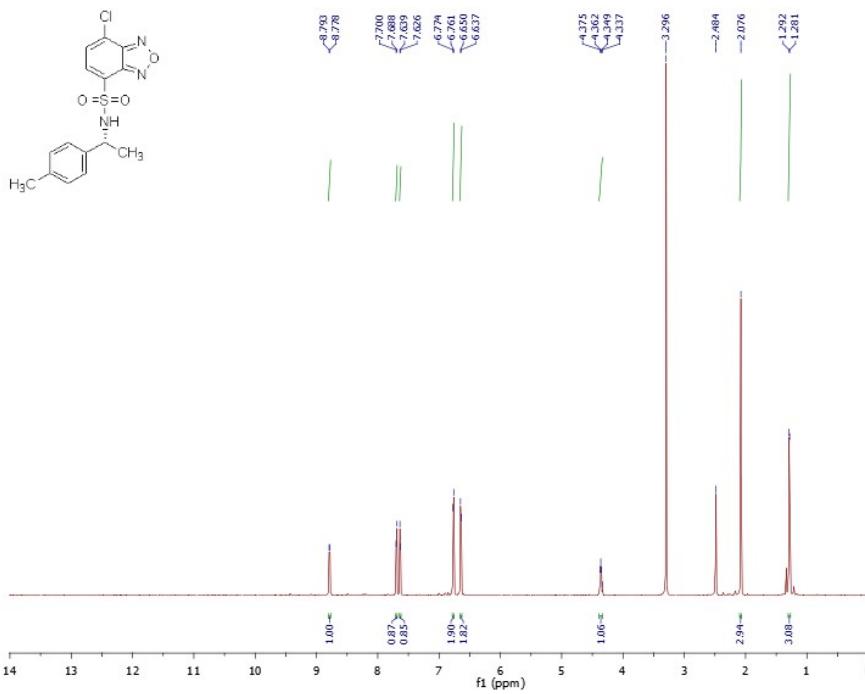
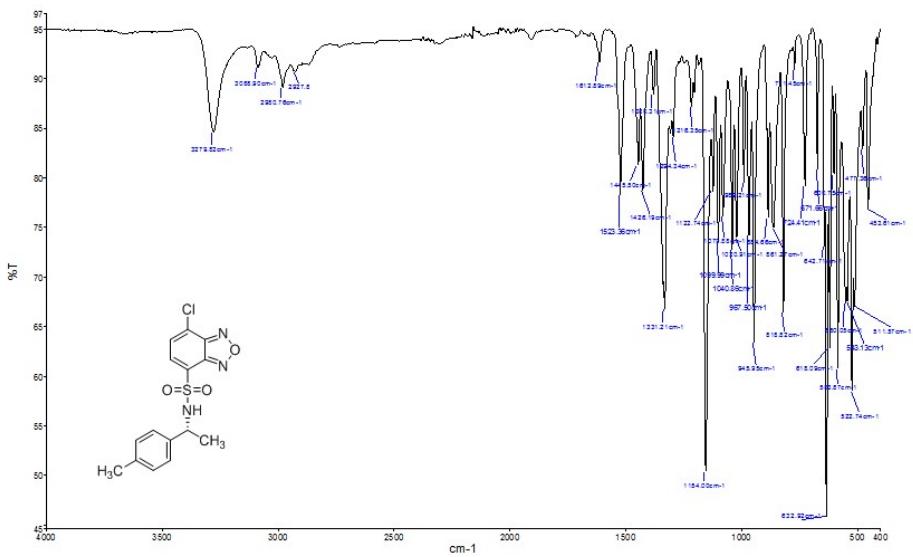


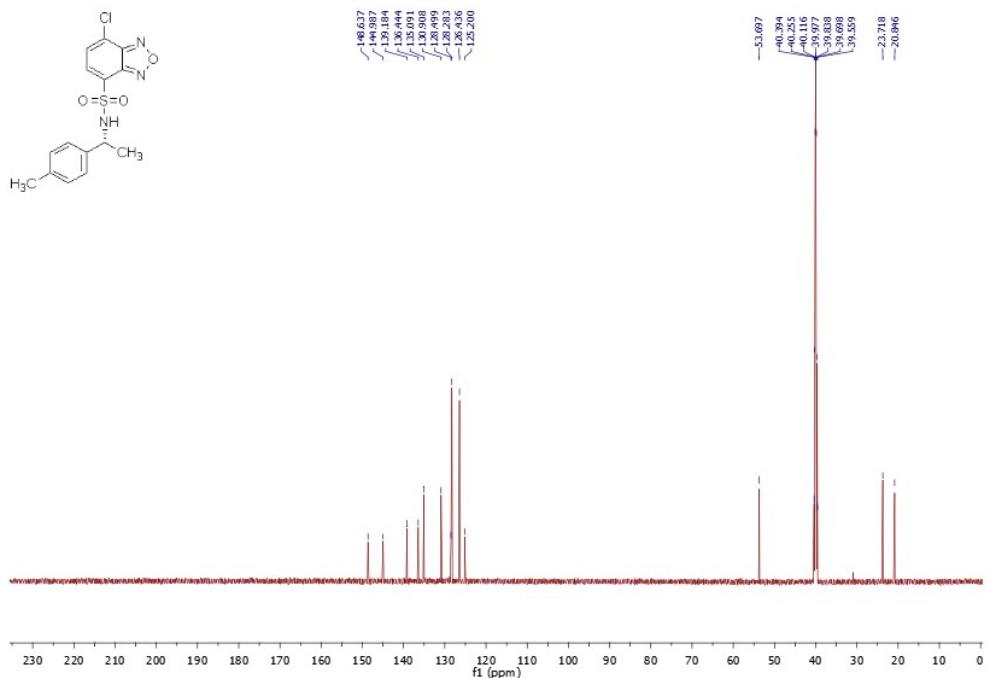
Compound 6b



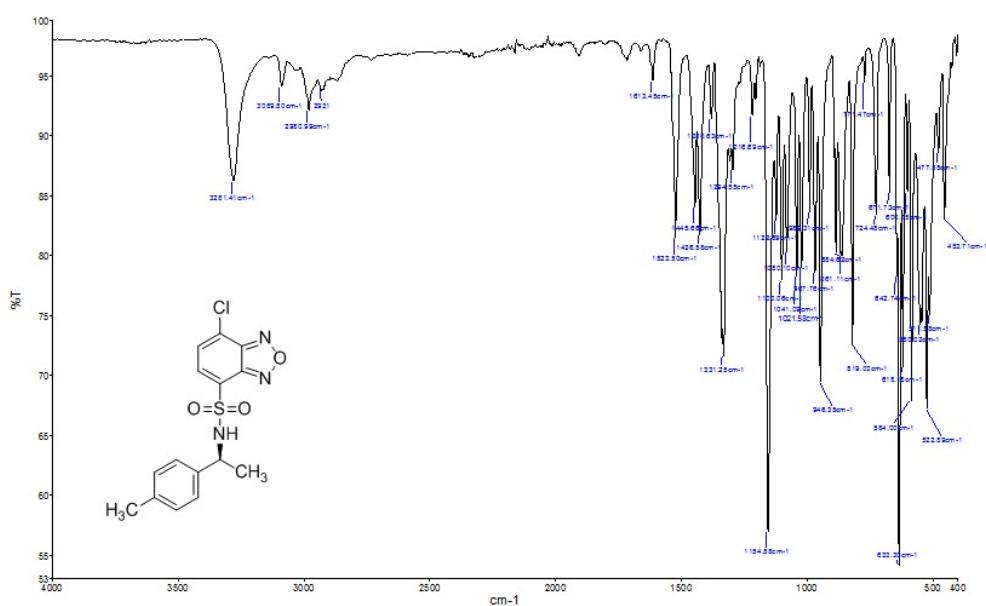


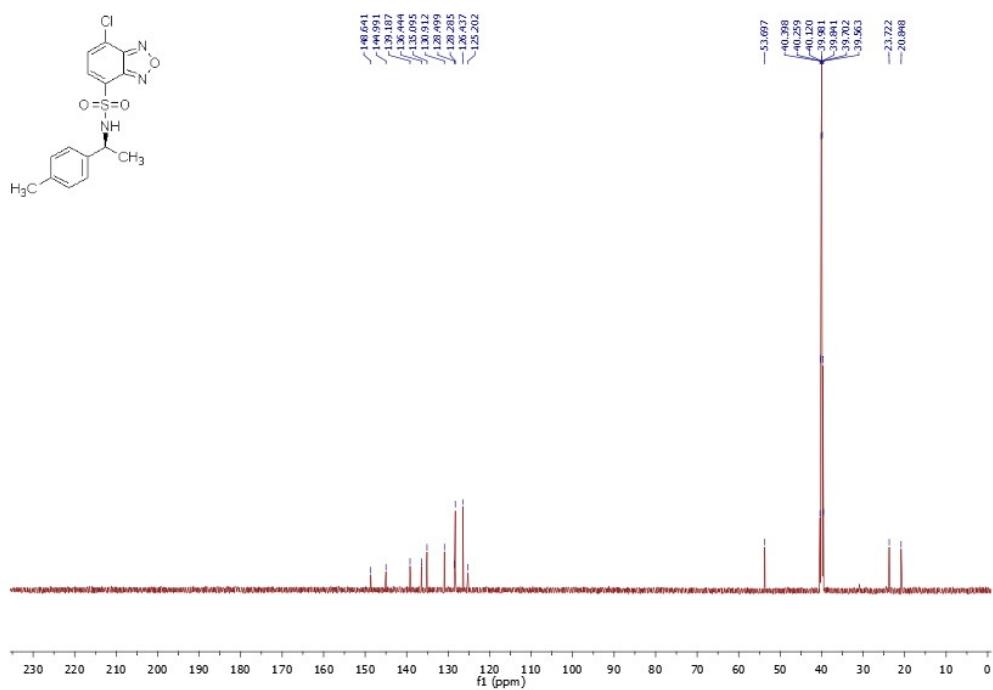
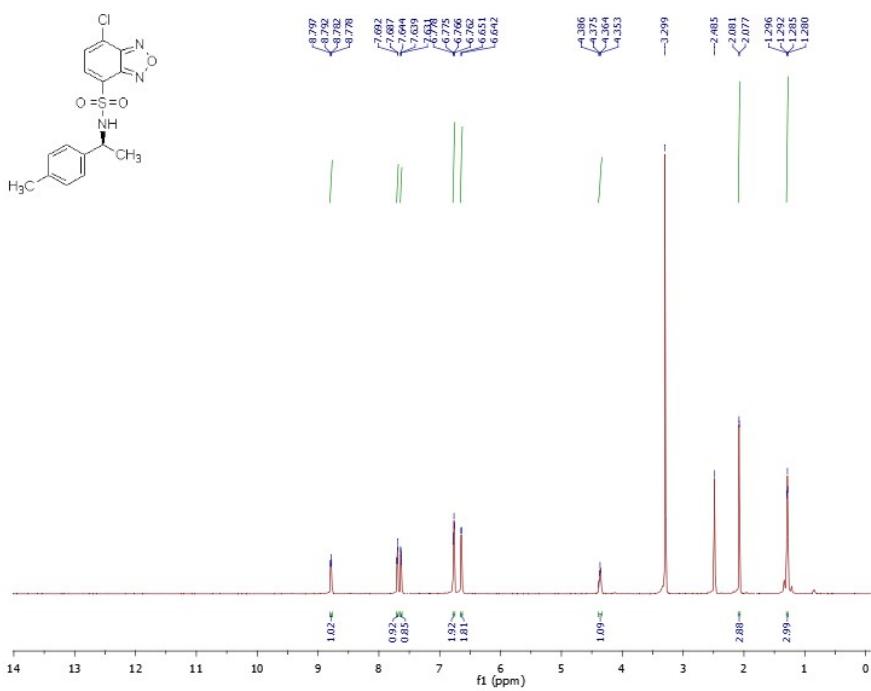
Compound 7a



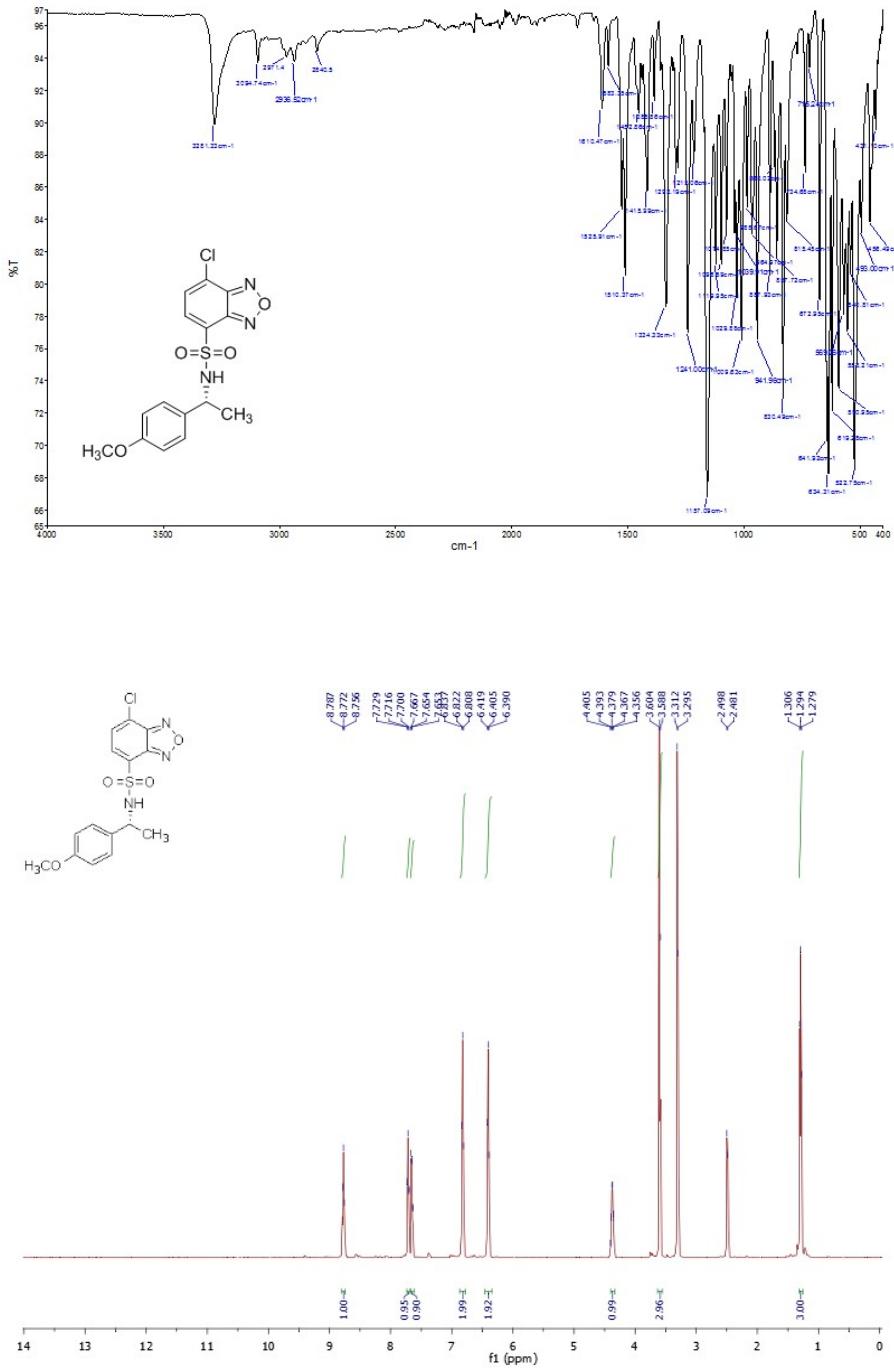


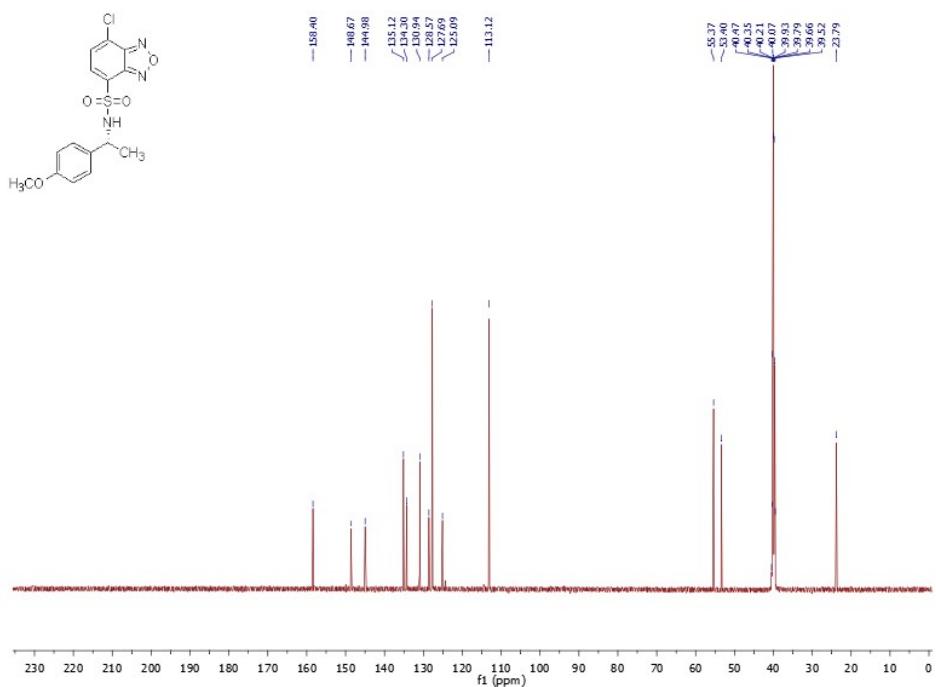
Compound 7b



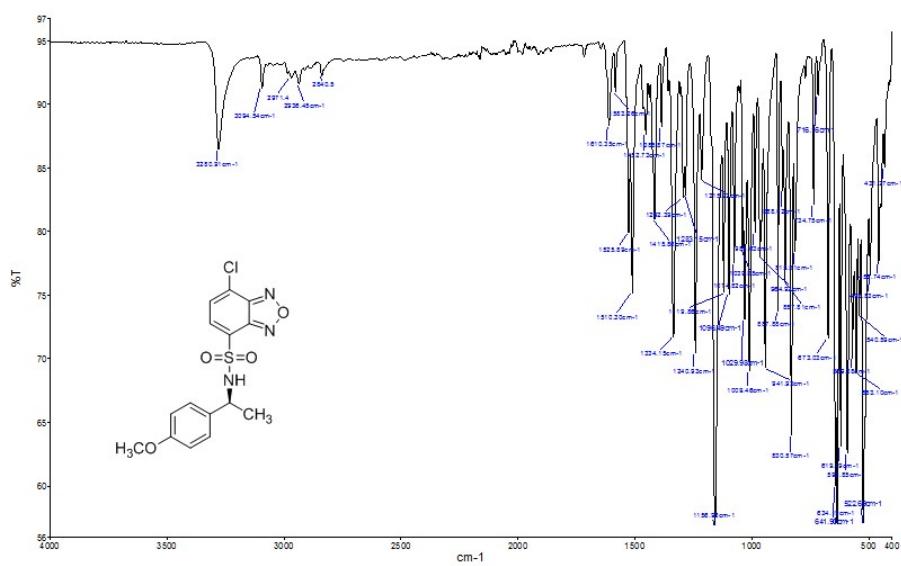


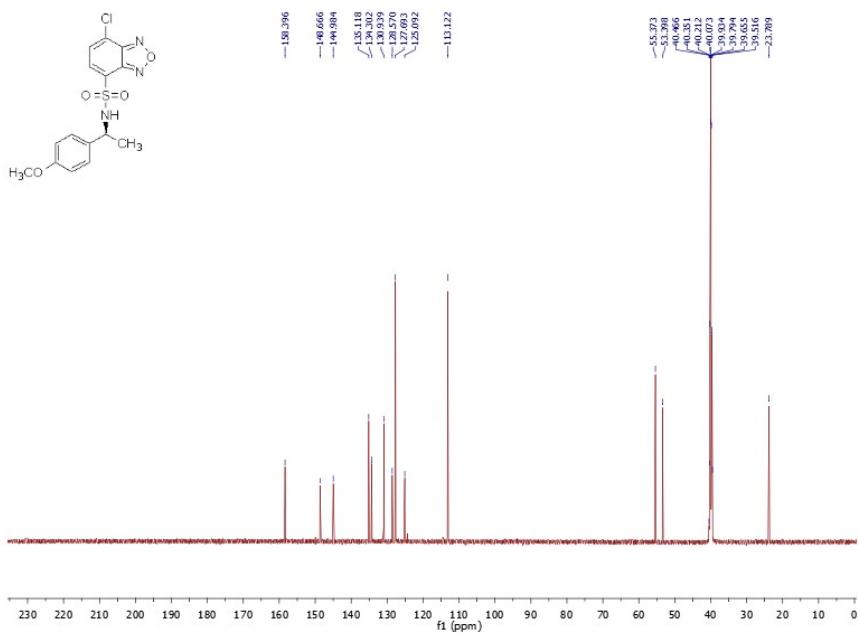
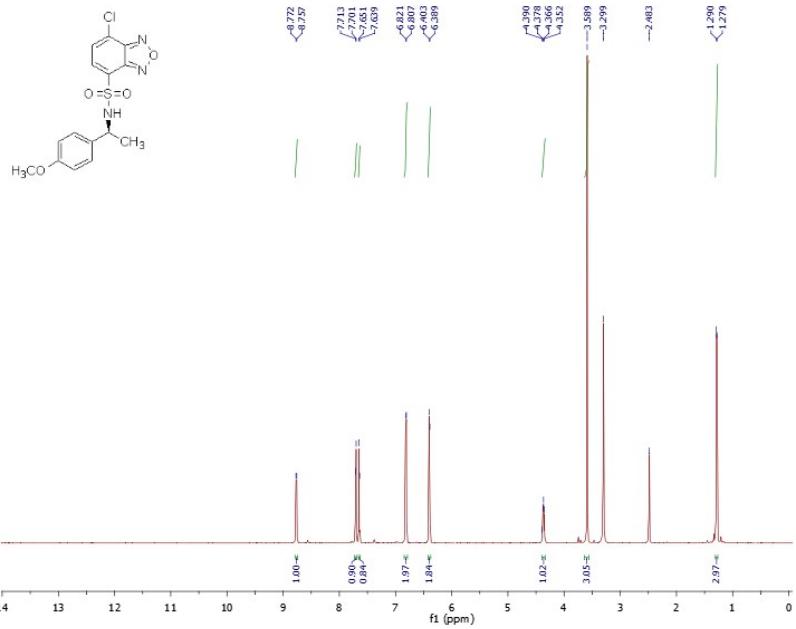
Compound 8a



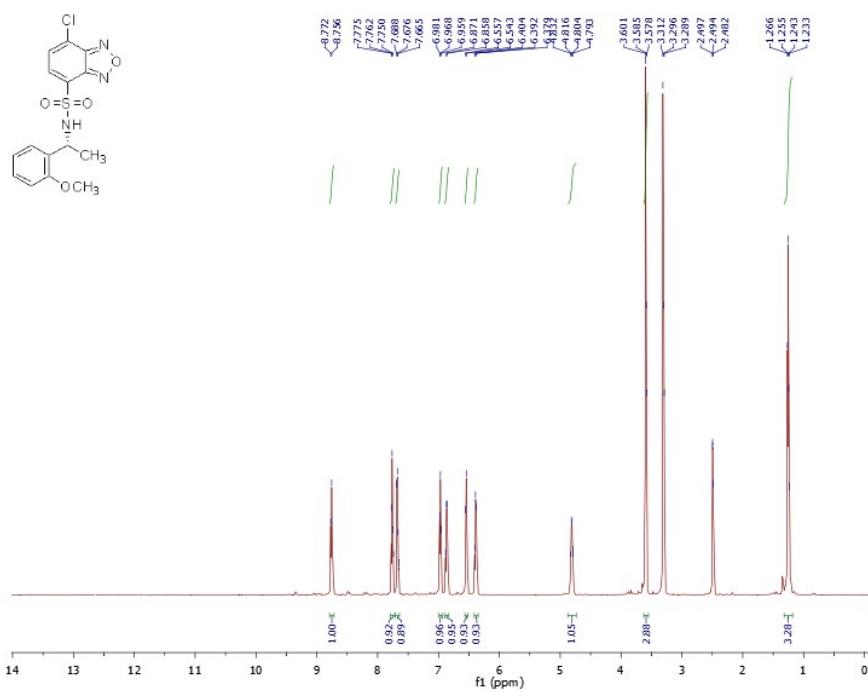
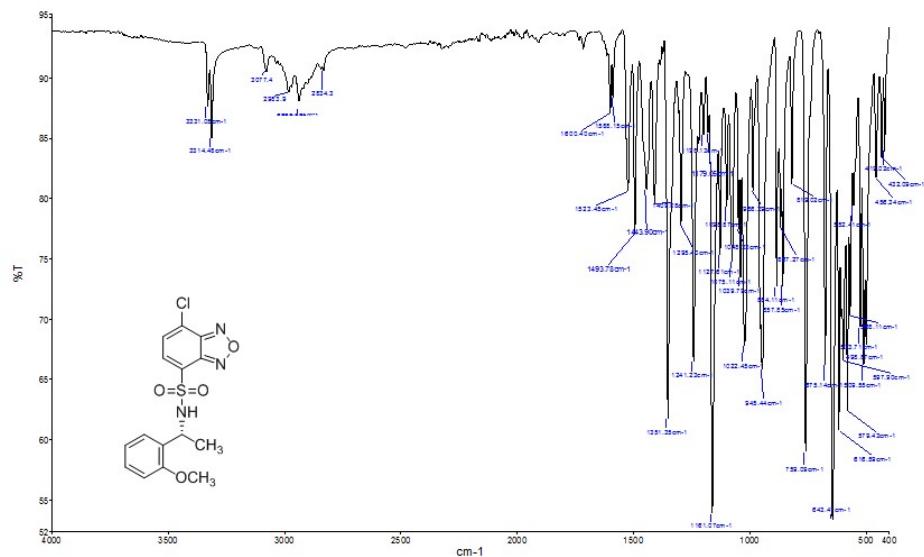


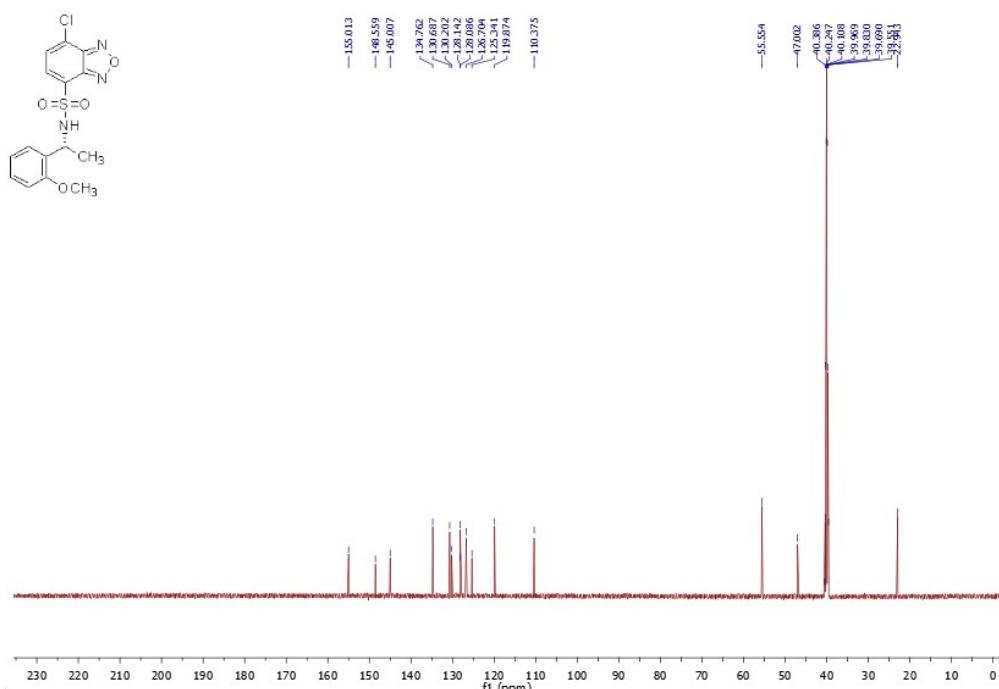
Compound 8b



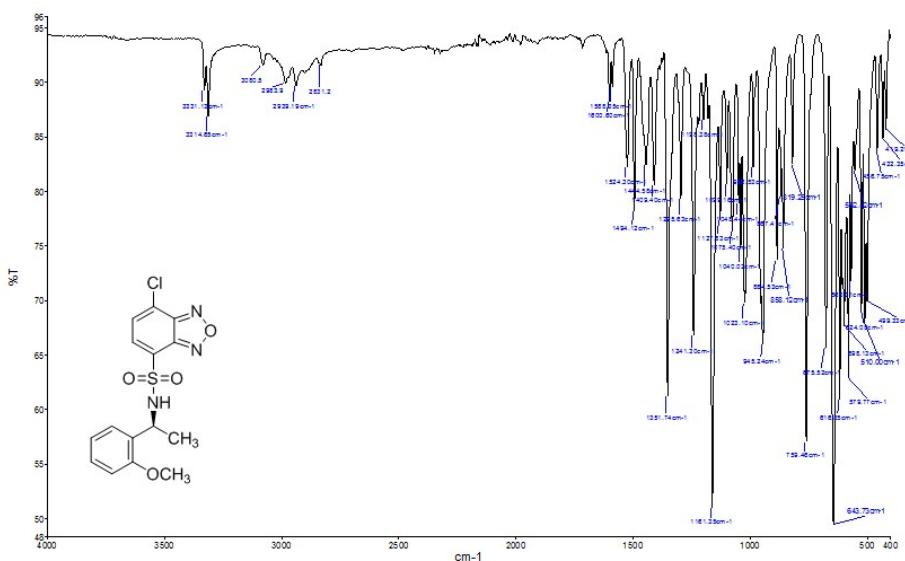


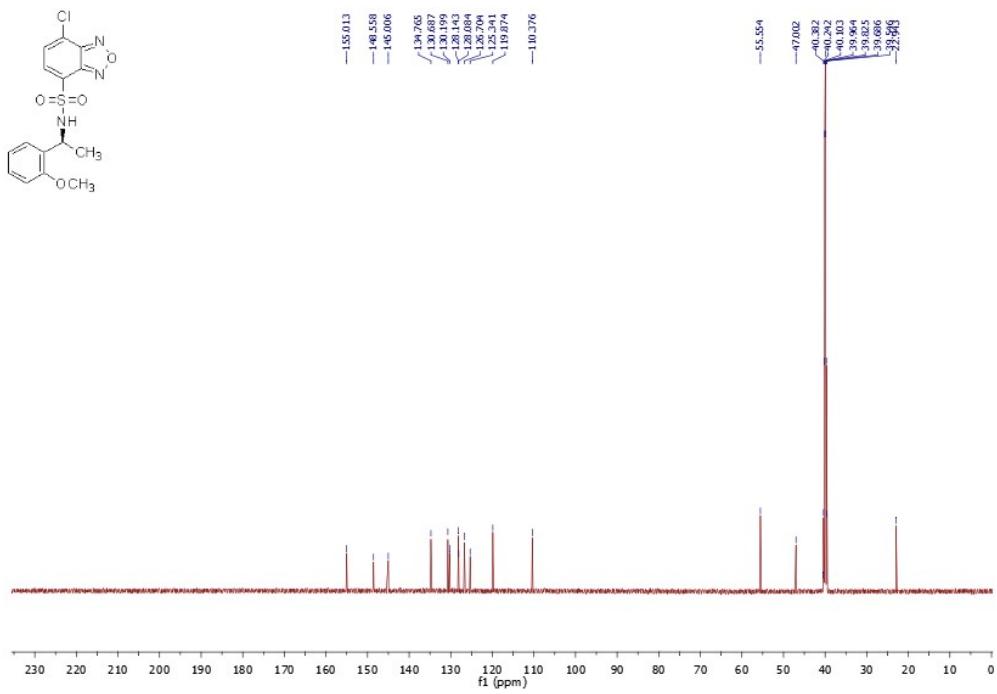
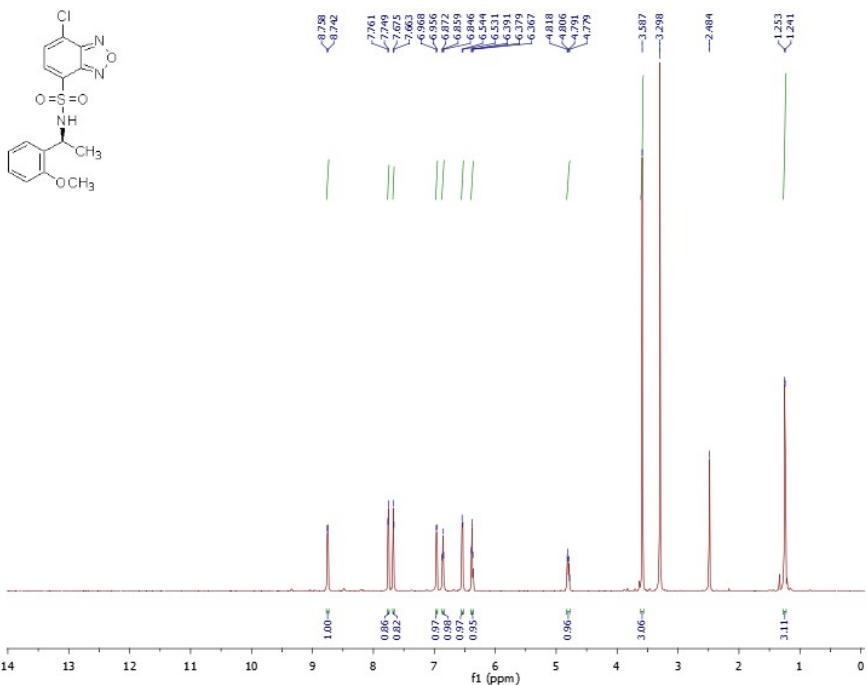
Compound 9a



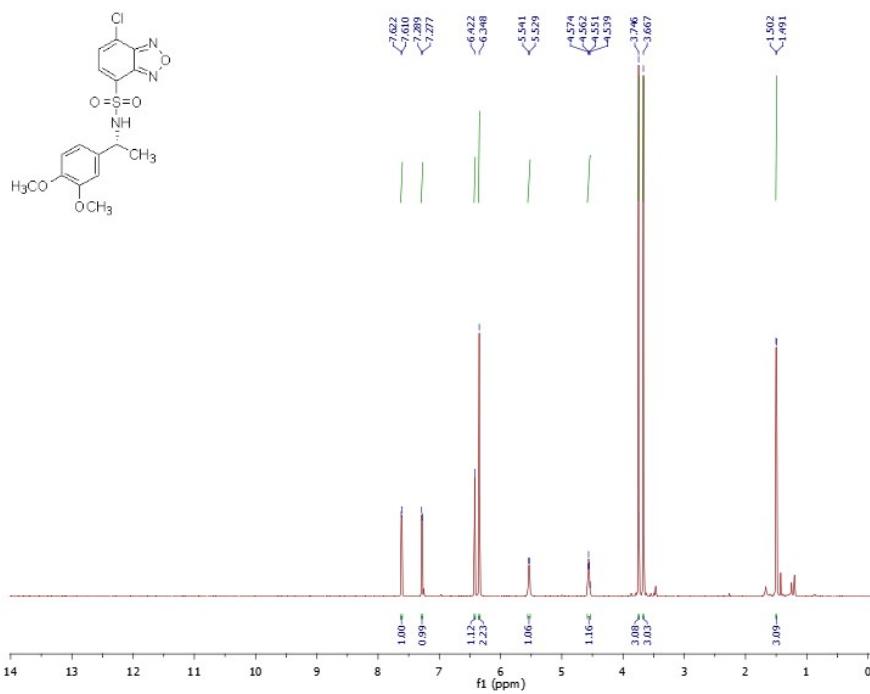
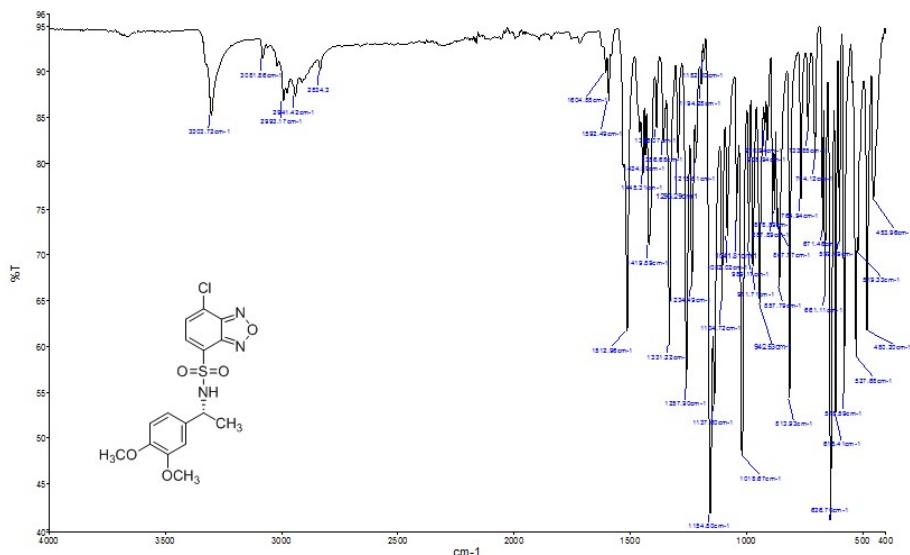


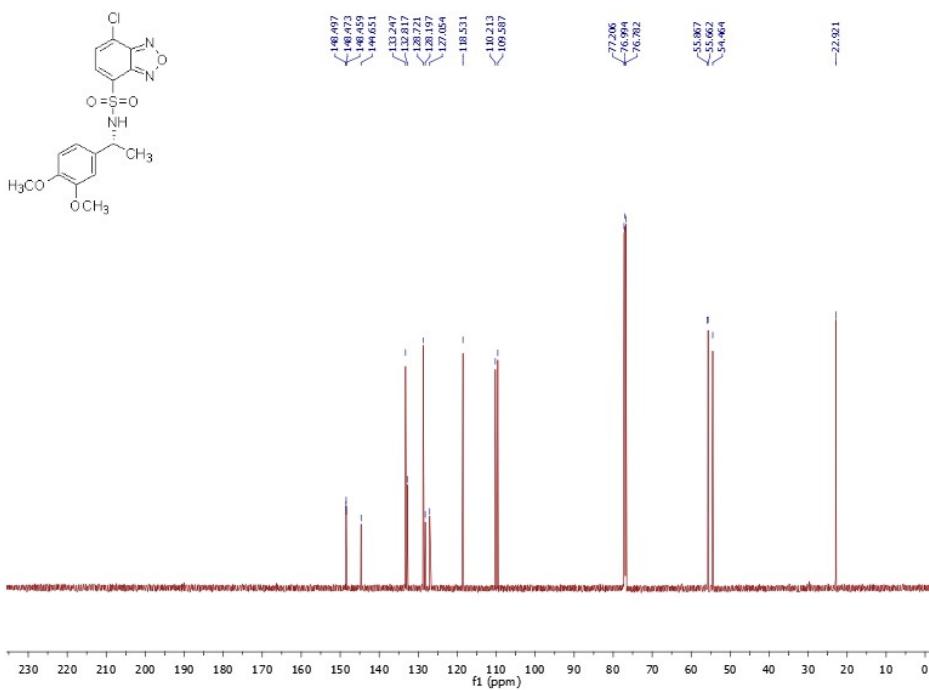
Compound 9b



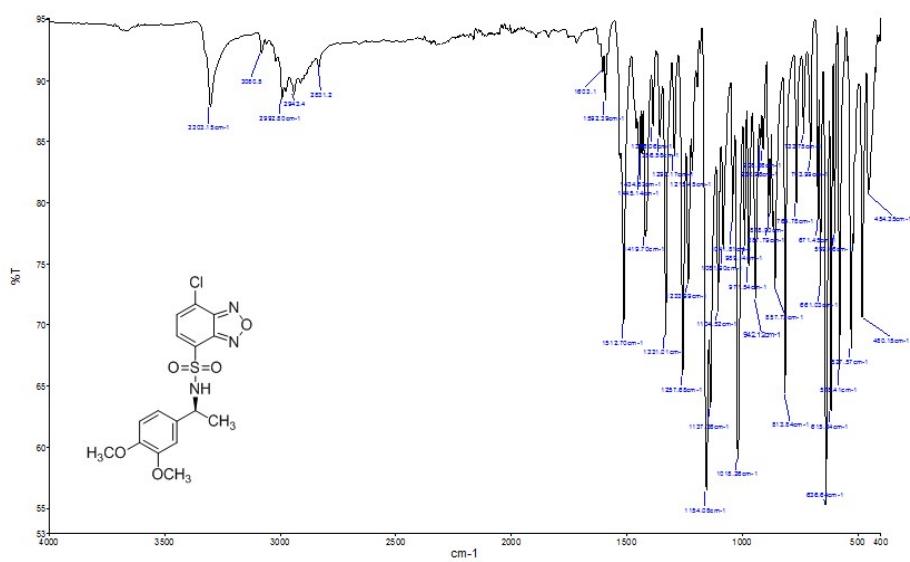


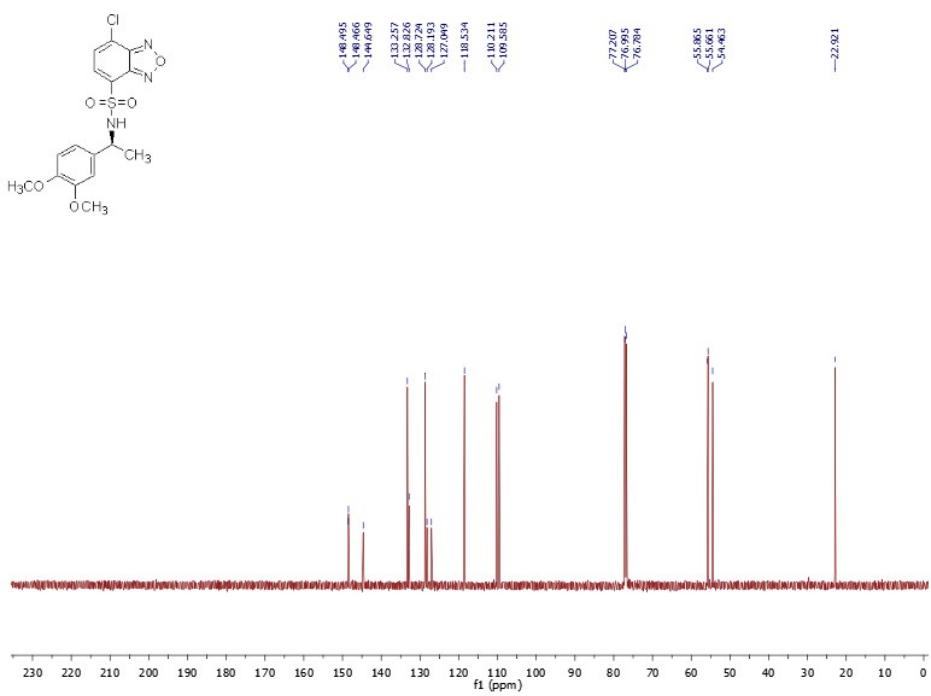
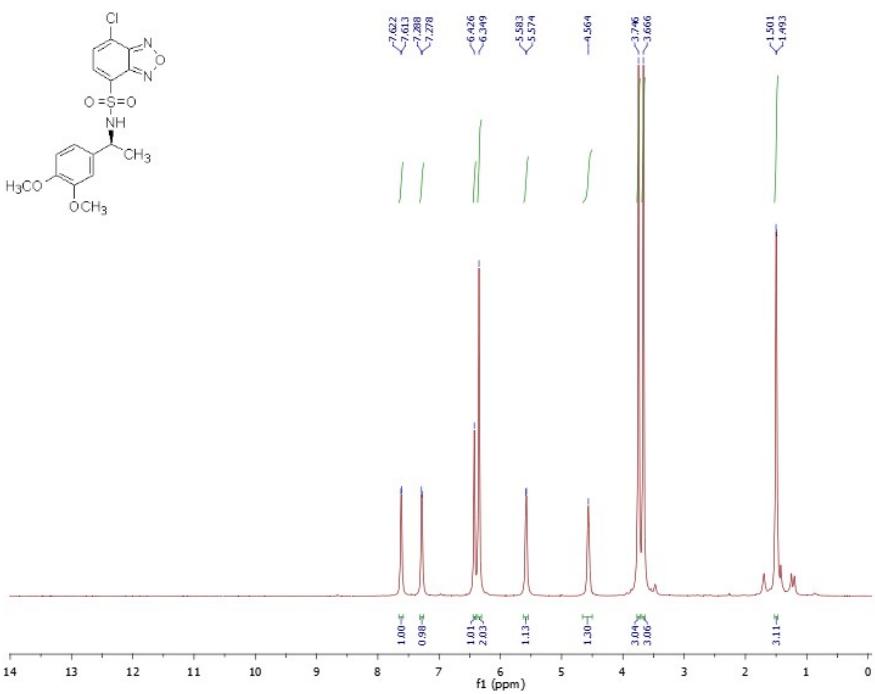
Compound 10a



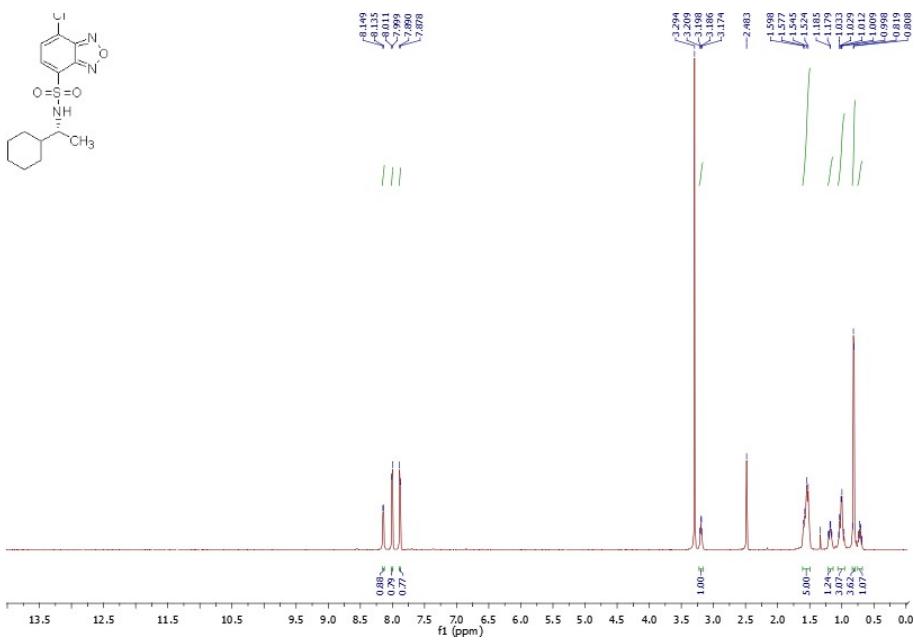
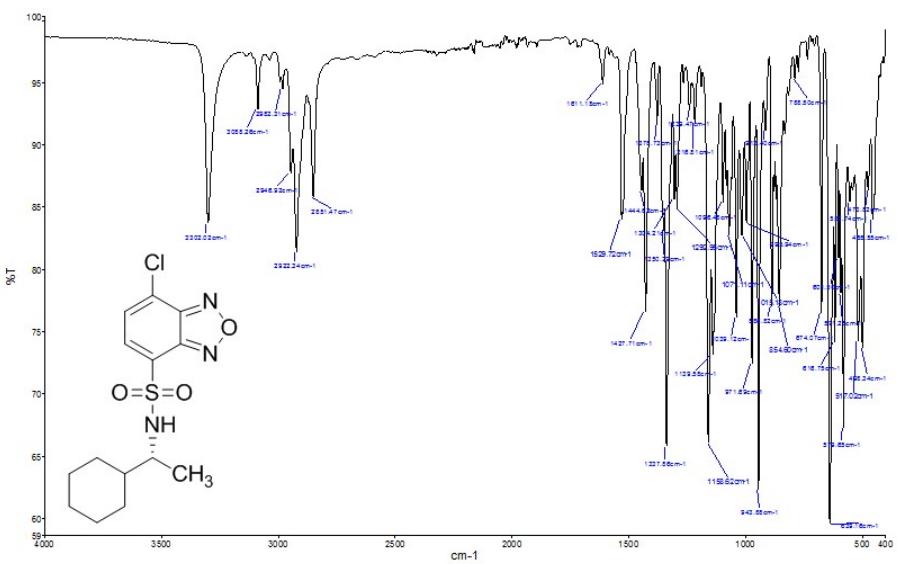


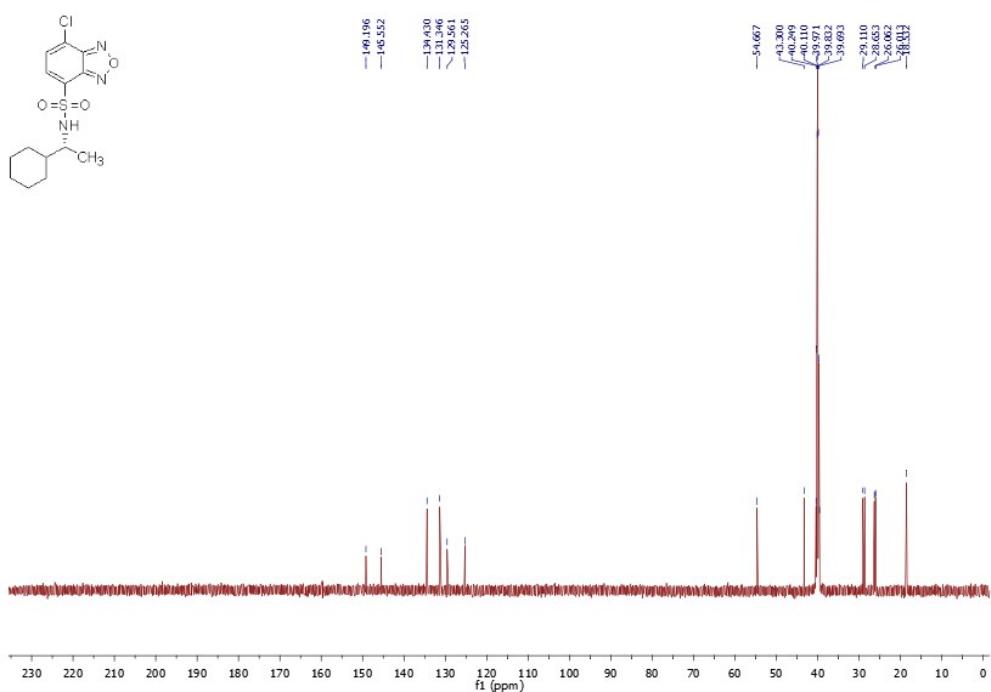
Compound 10b



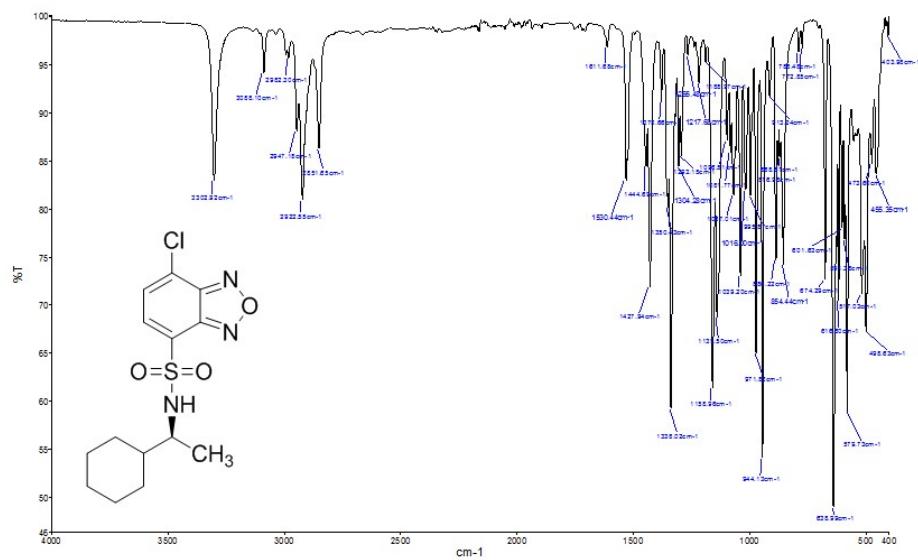


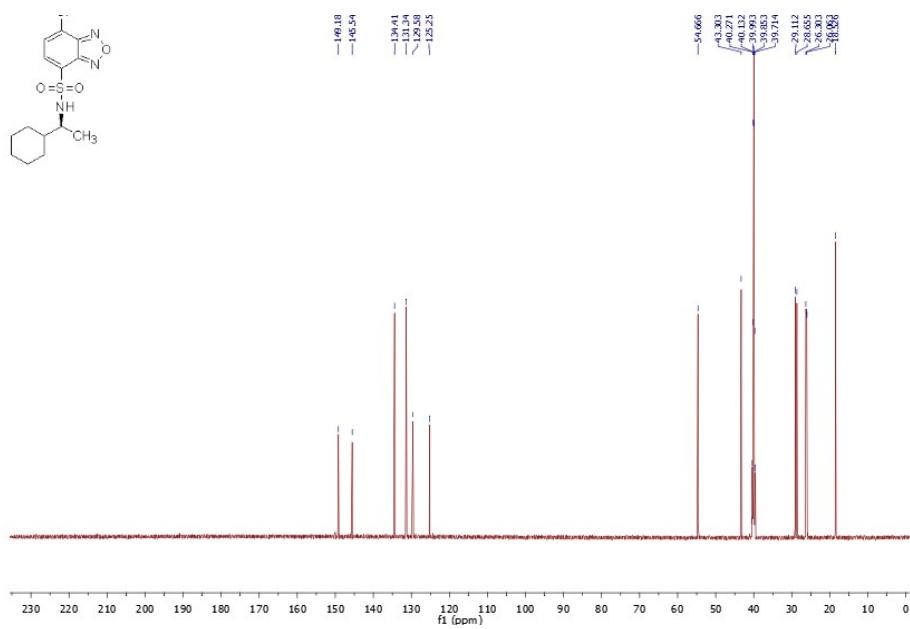
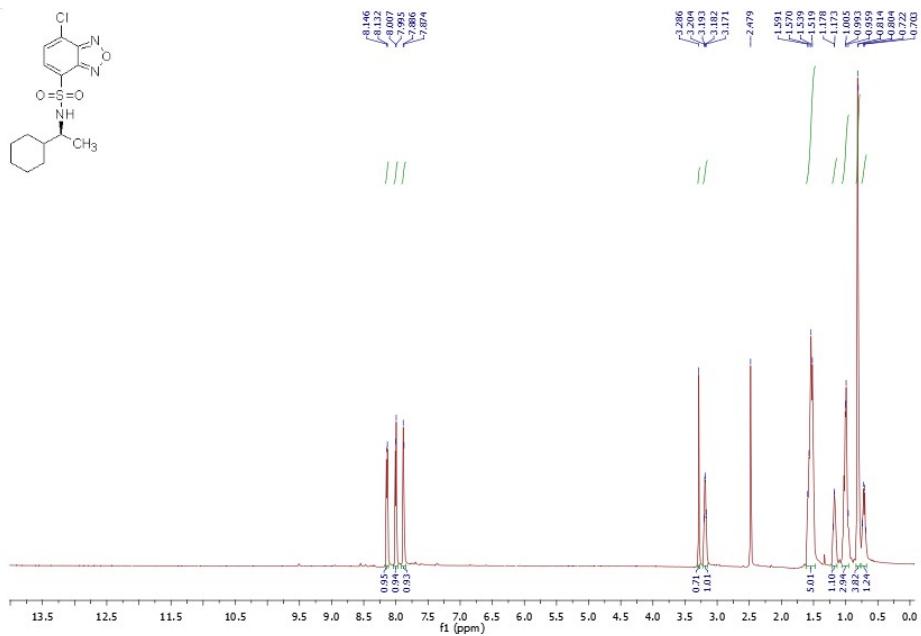
Compound 11a



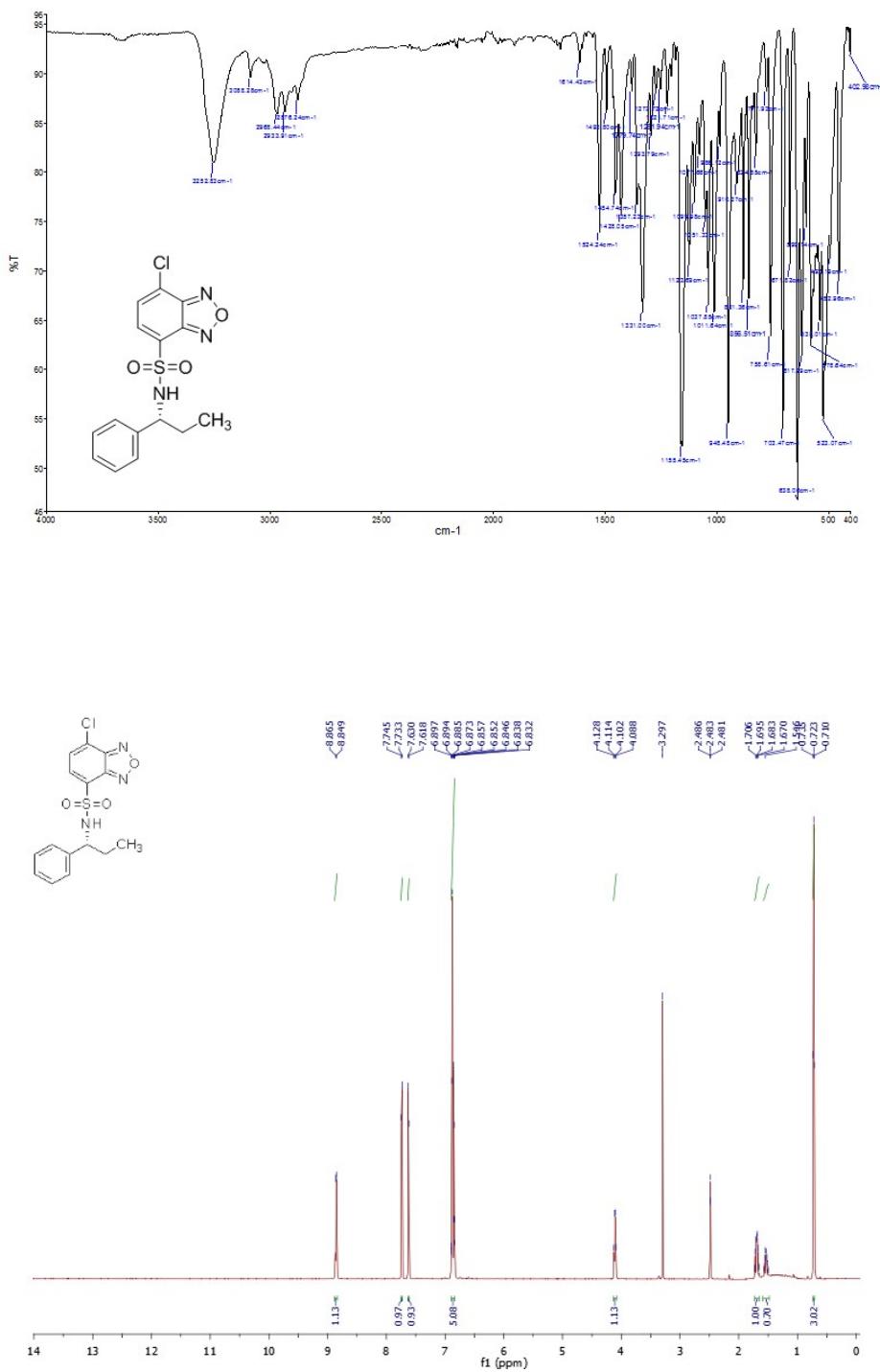


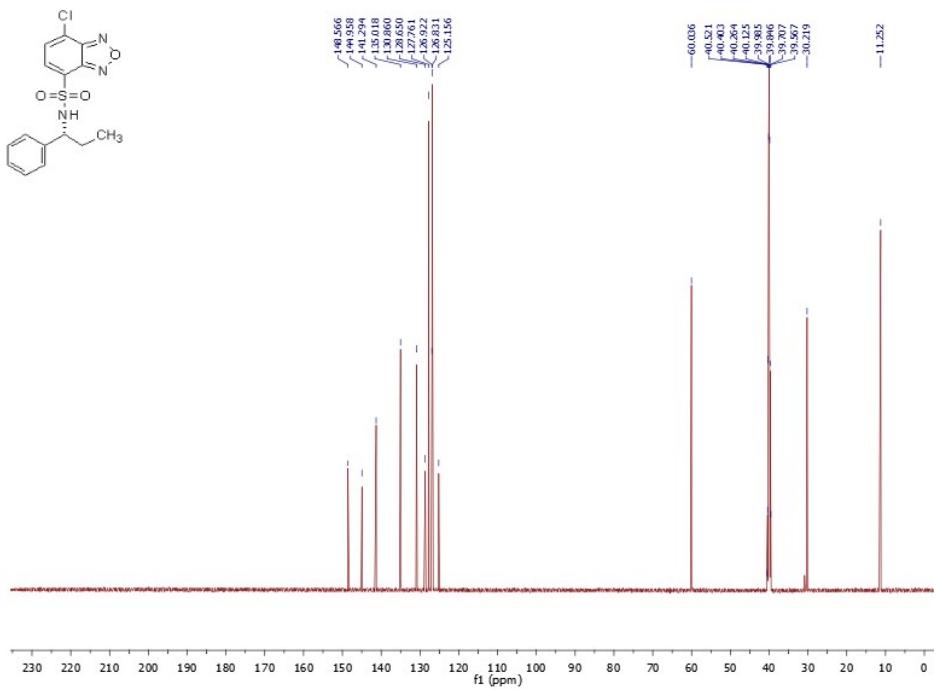
Compound 11b



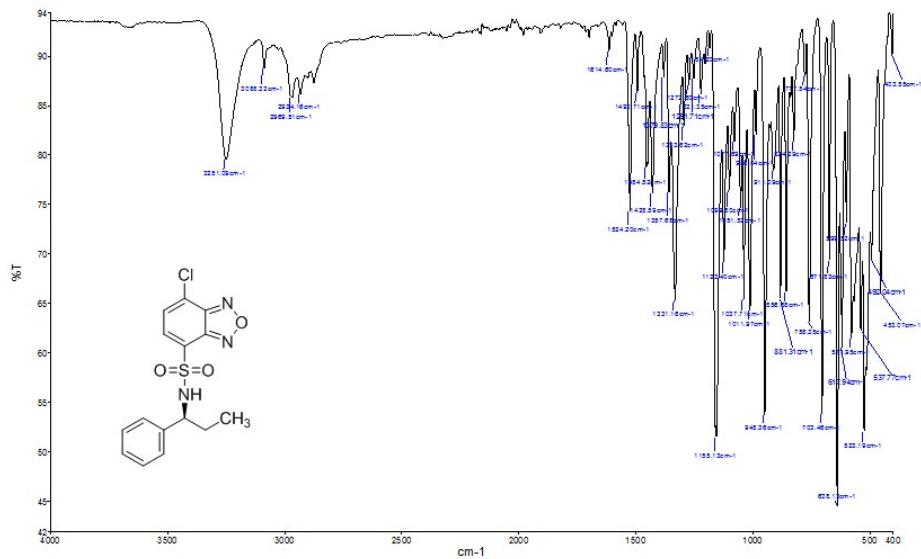


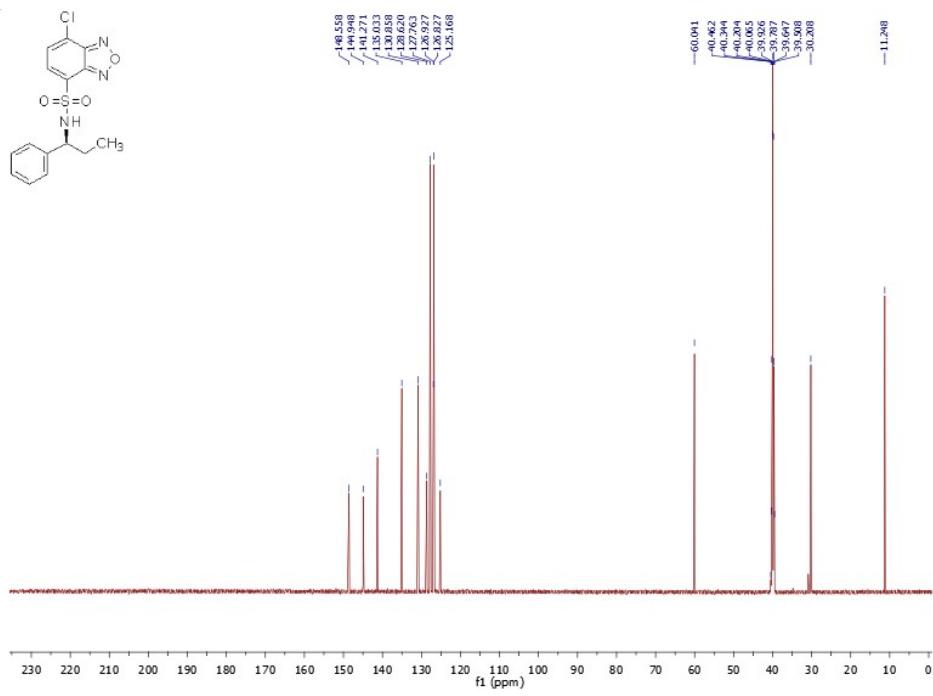
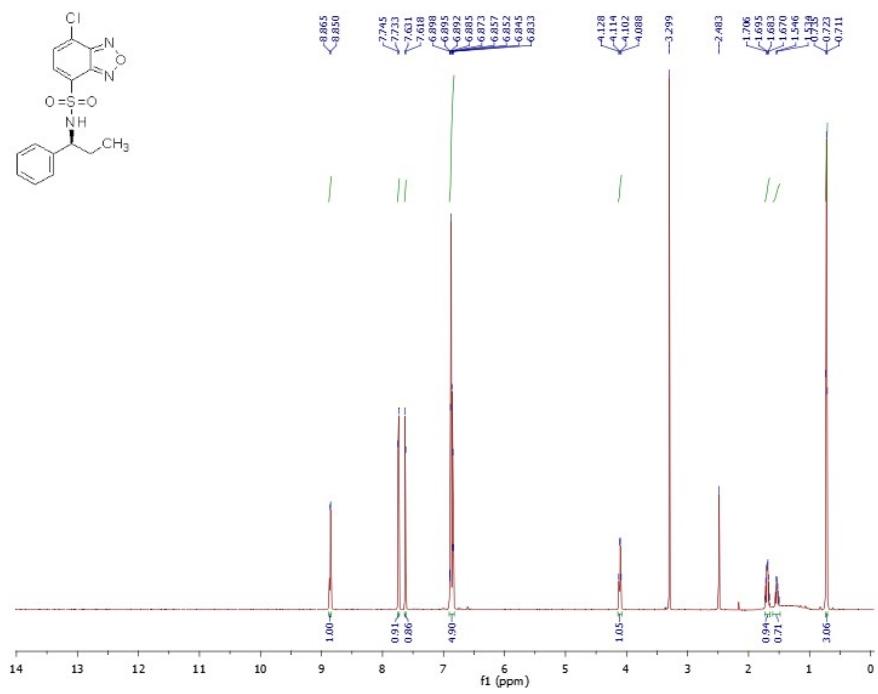
Compound 12a



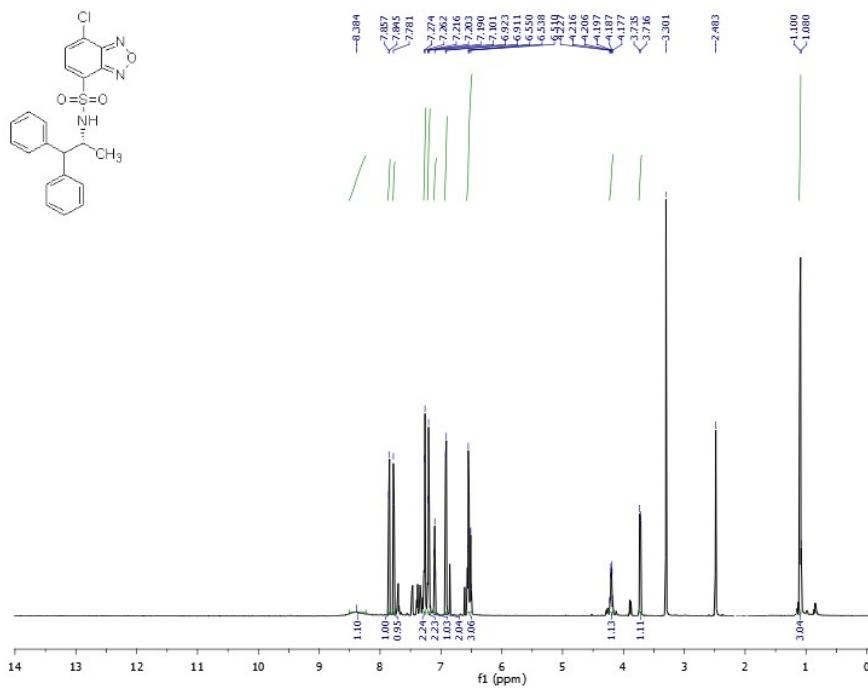
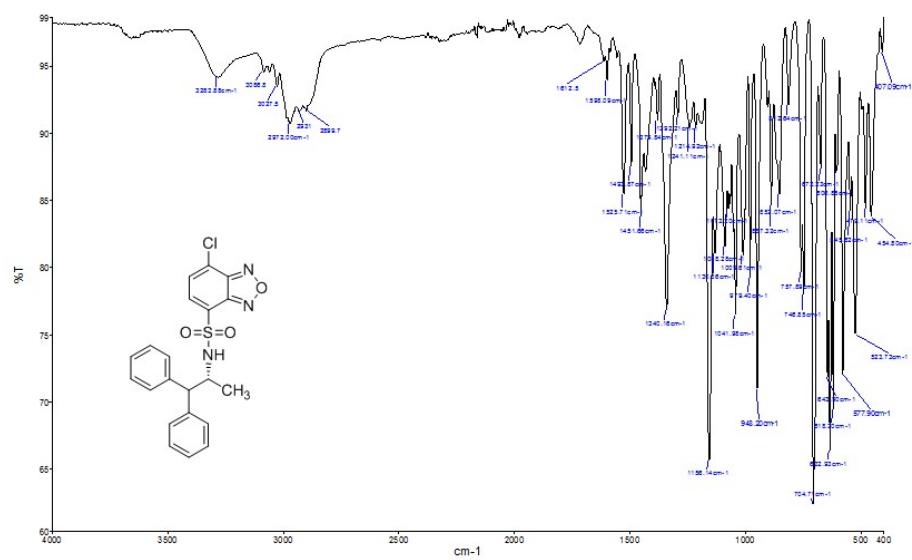


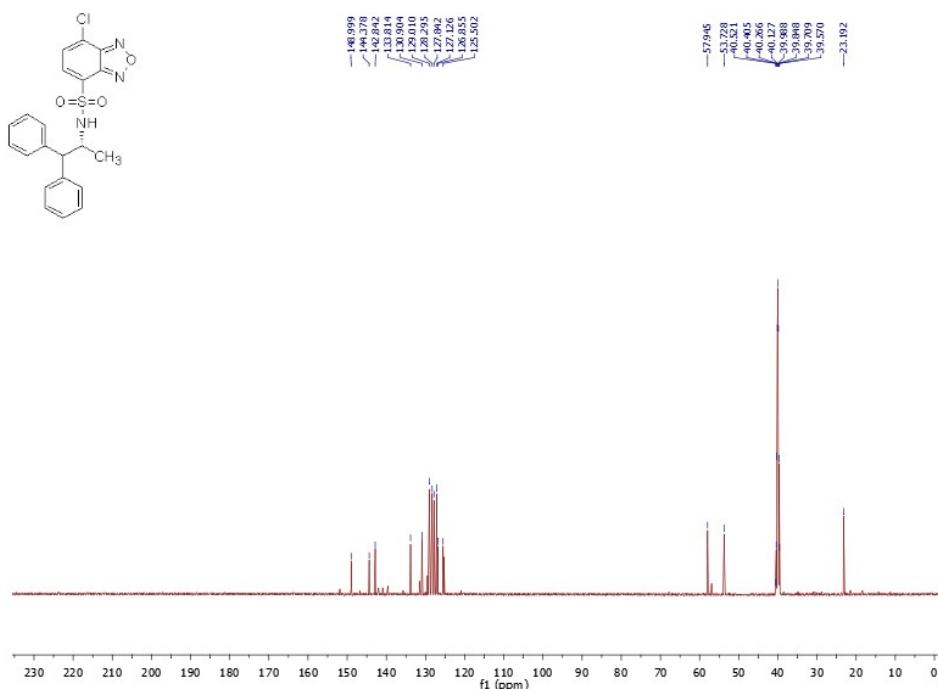
Compound 12b



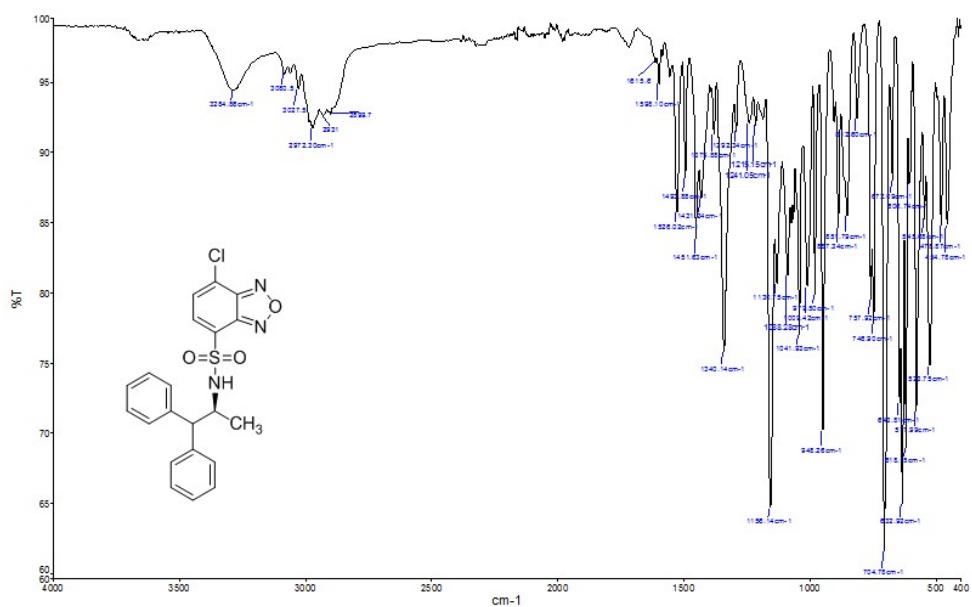


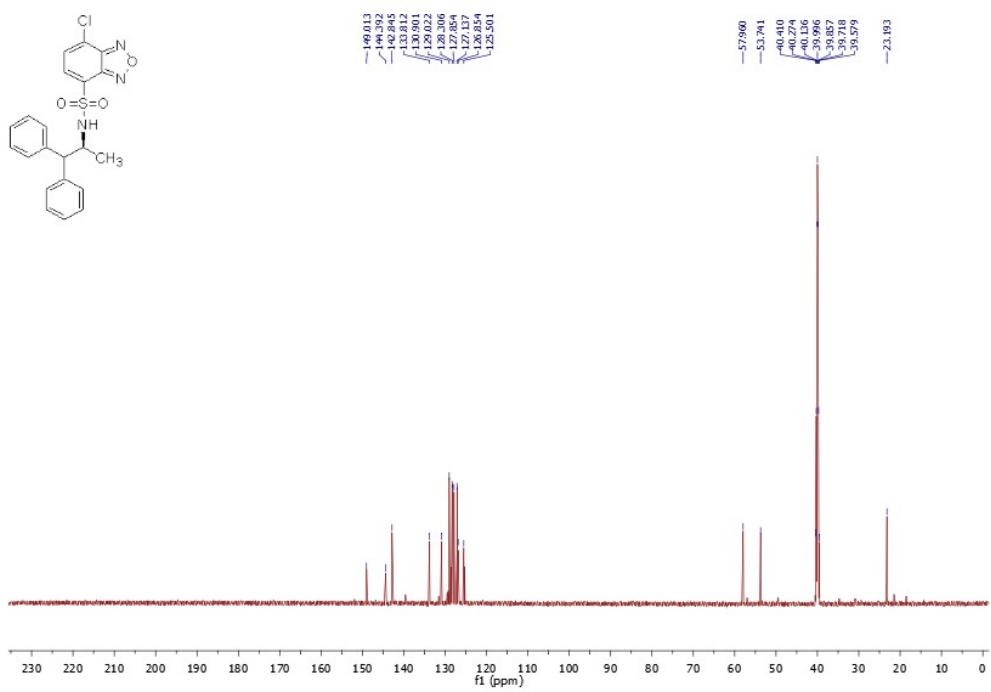
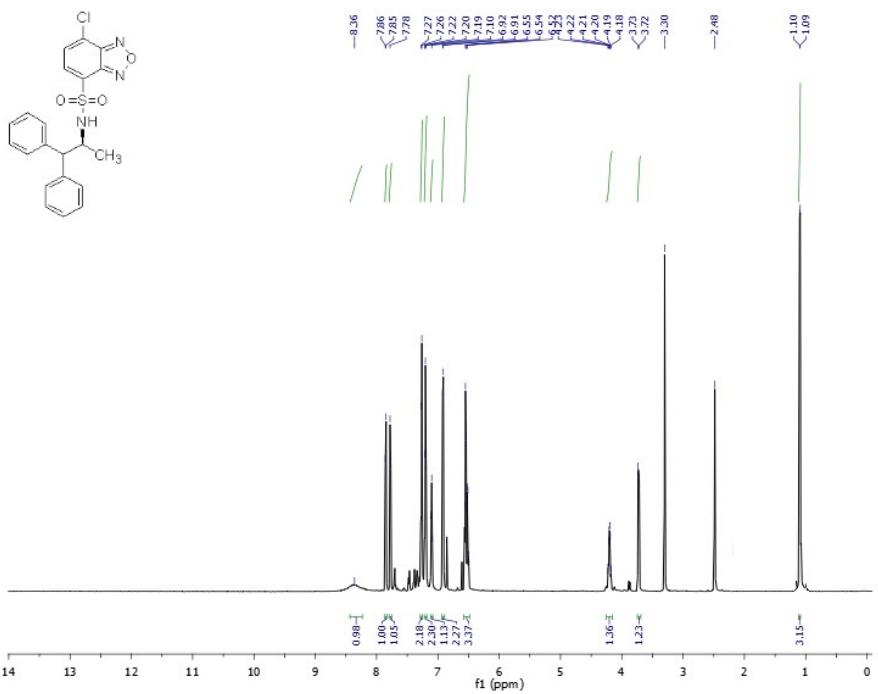
Compound 13a



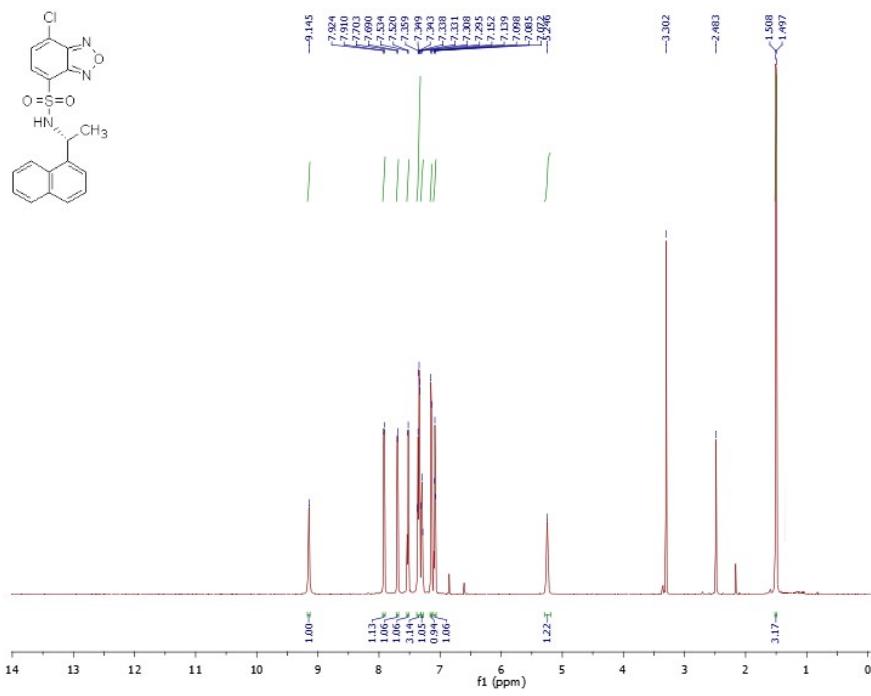
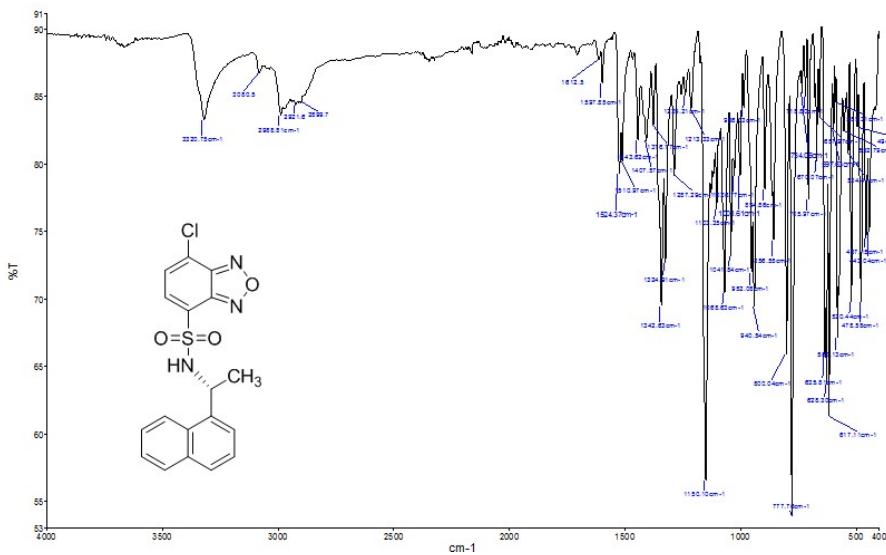


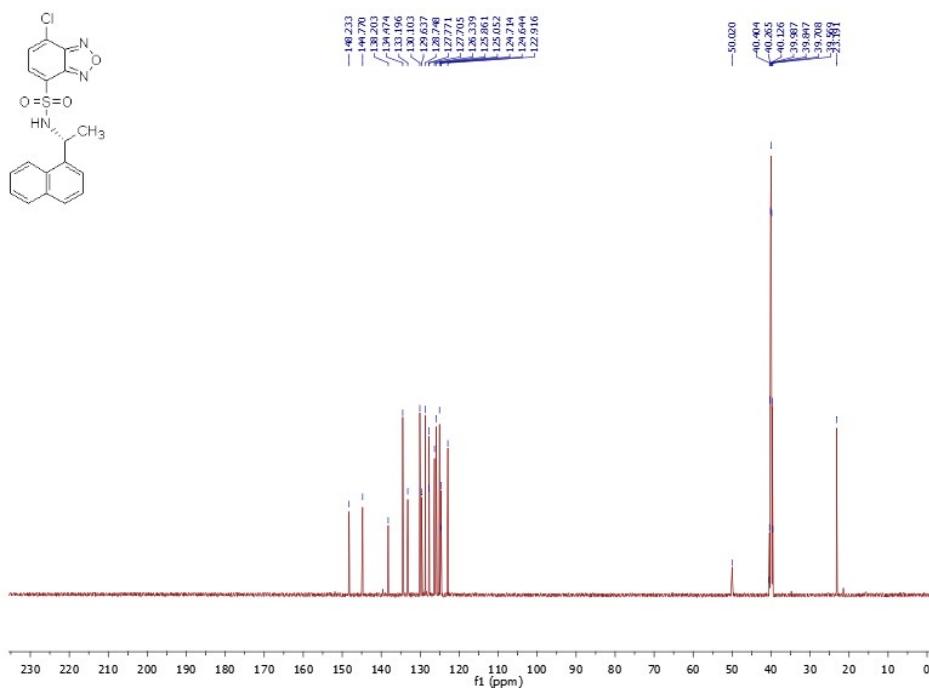
Compound 13b



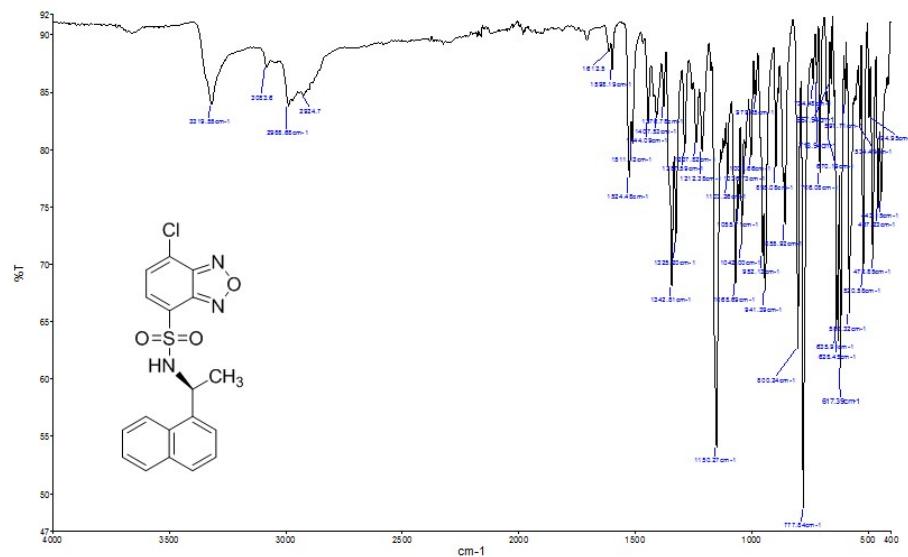


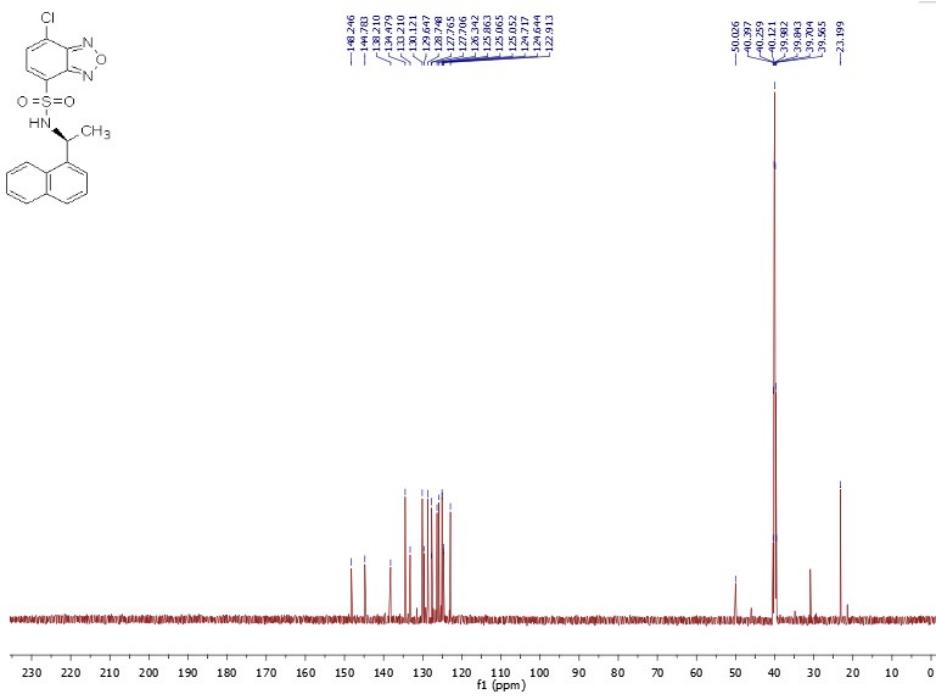
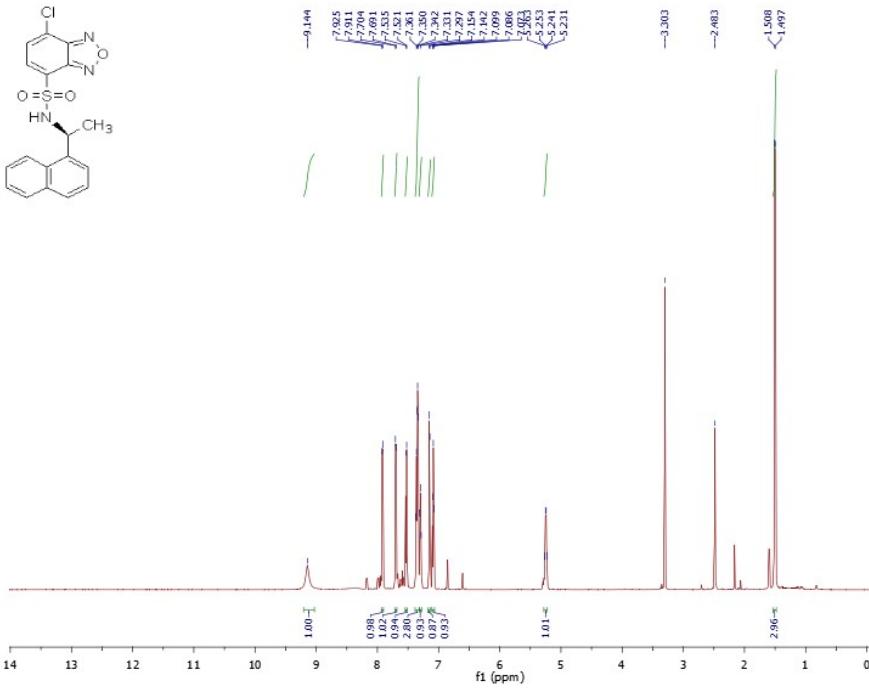
Compound 14a



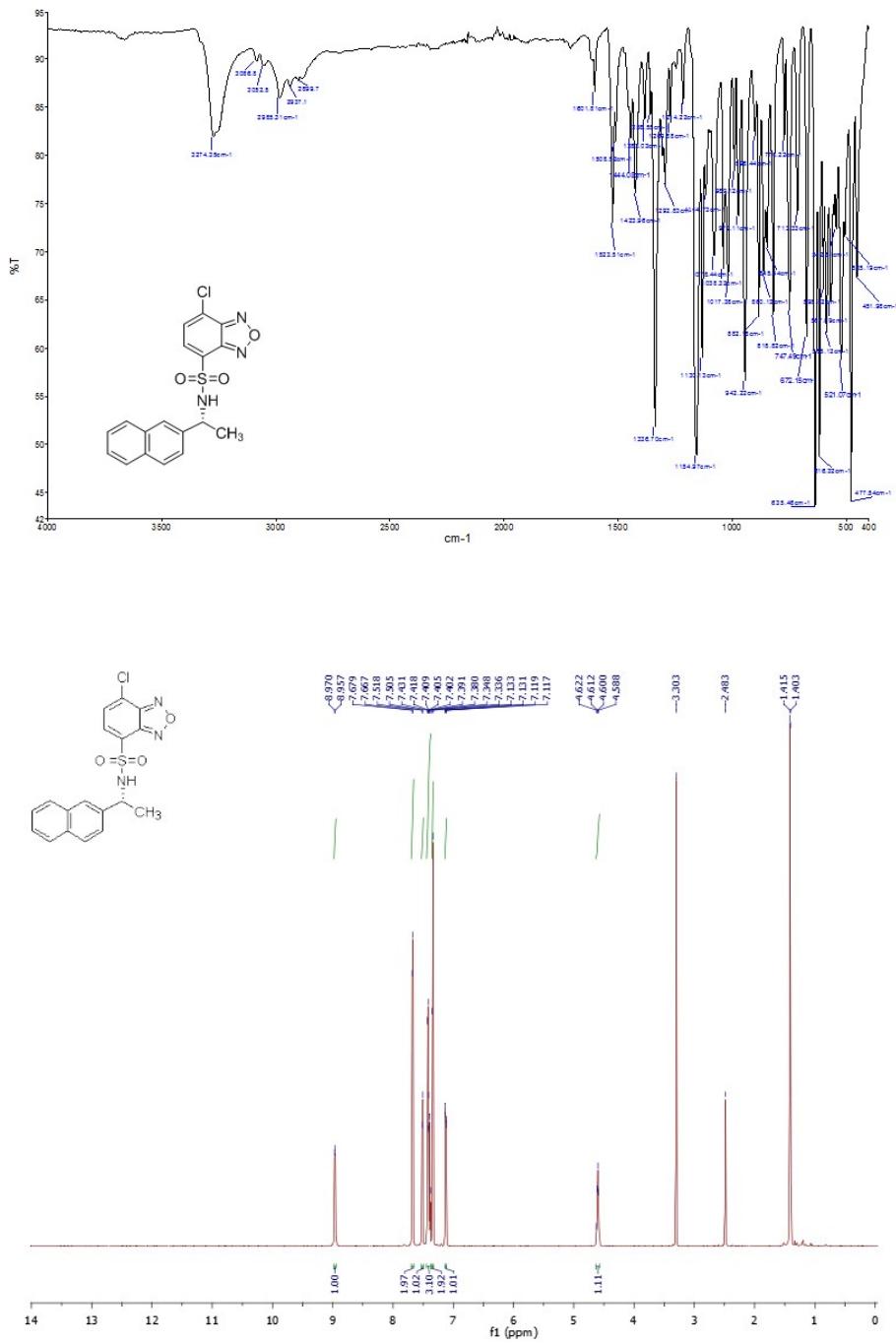


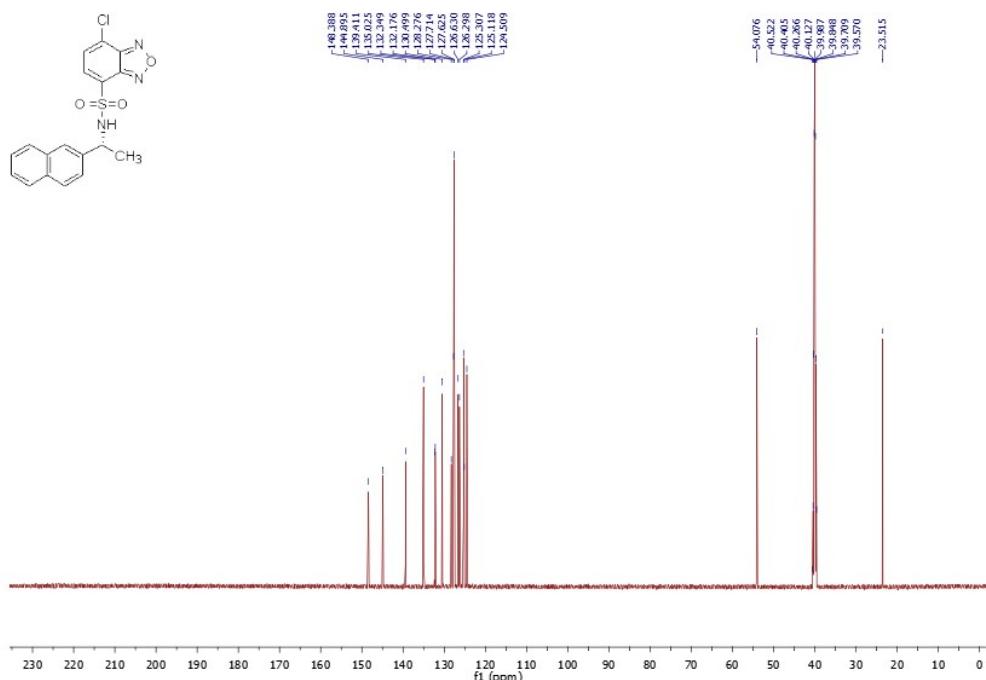
Compound 14b



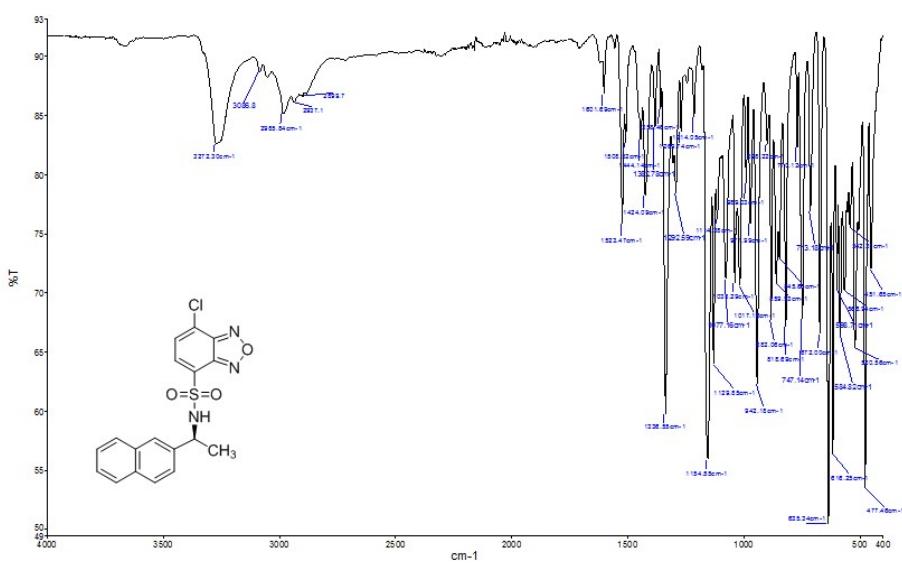


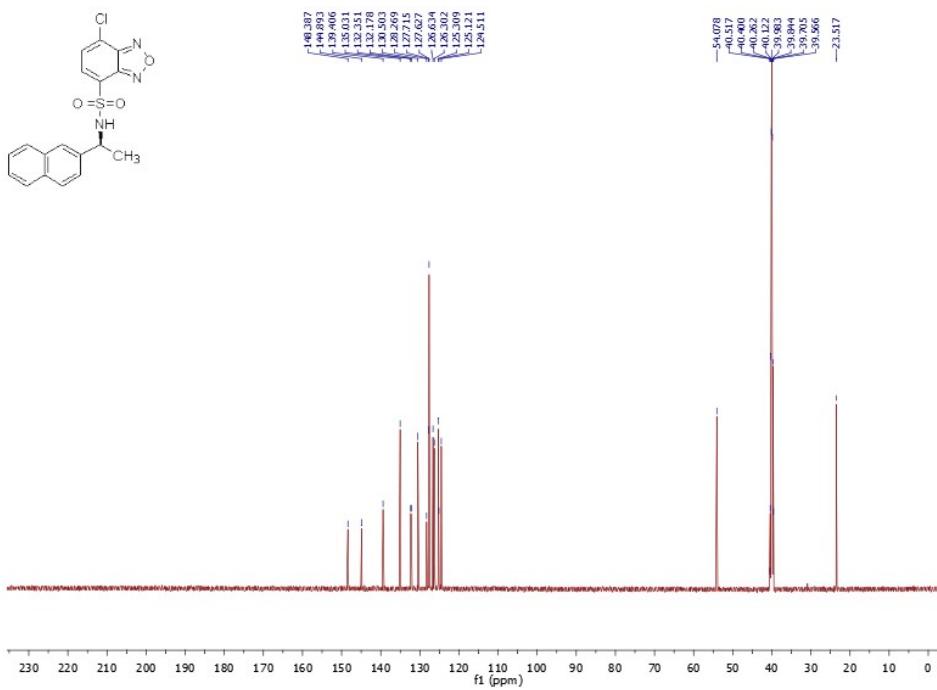
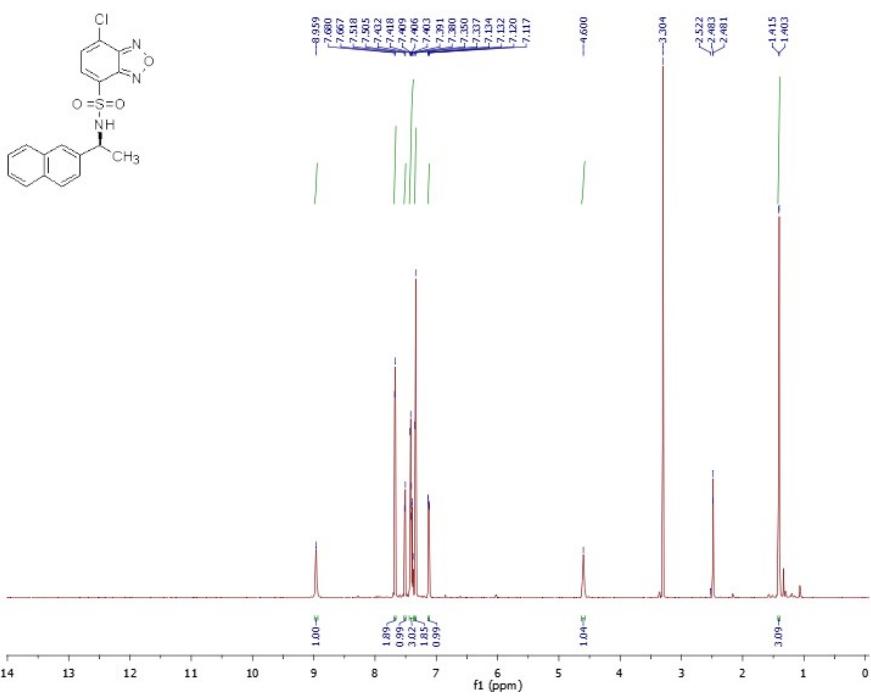
Compound 15a



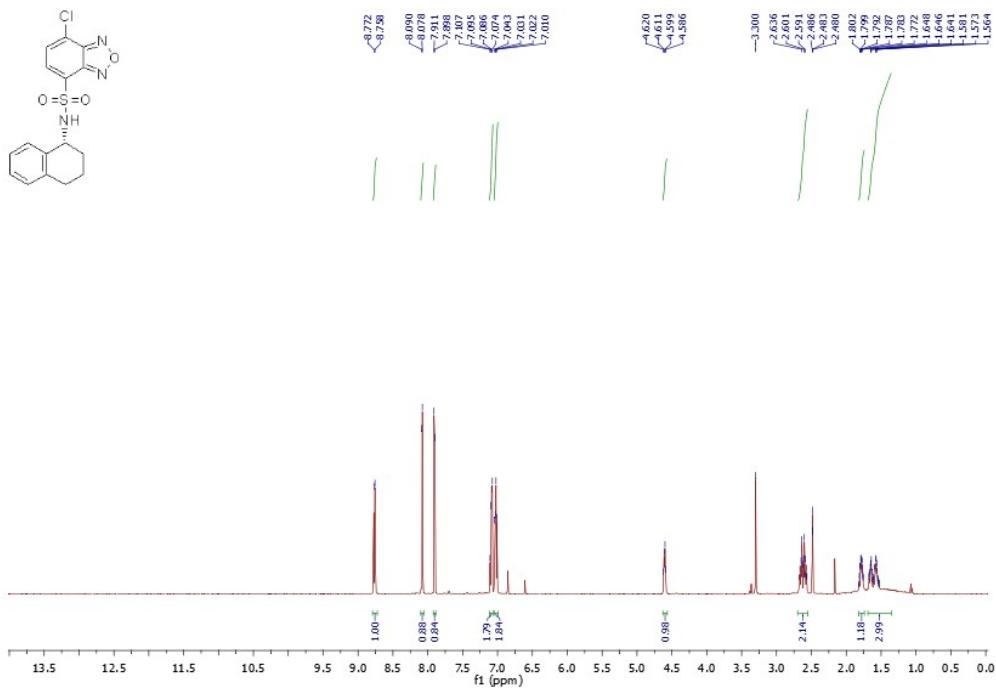
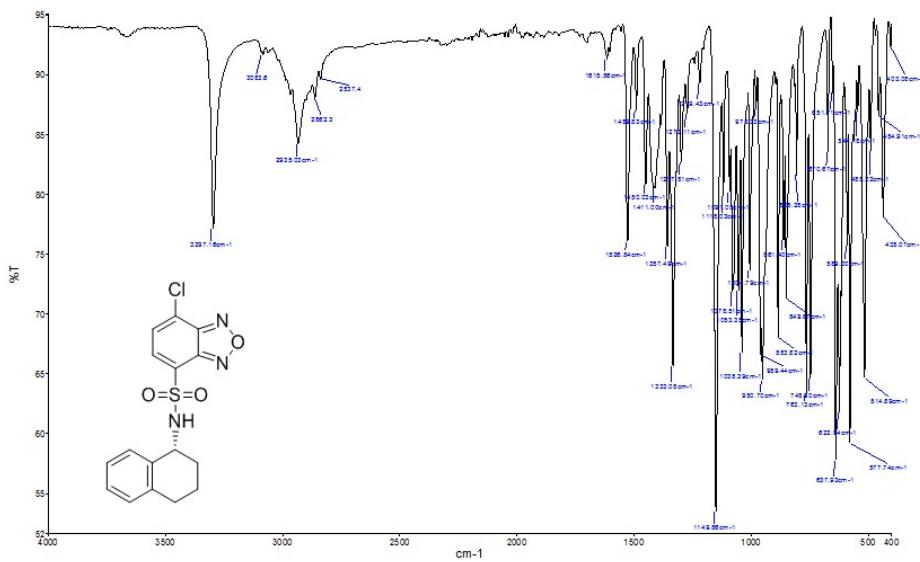


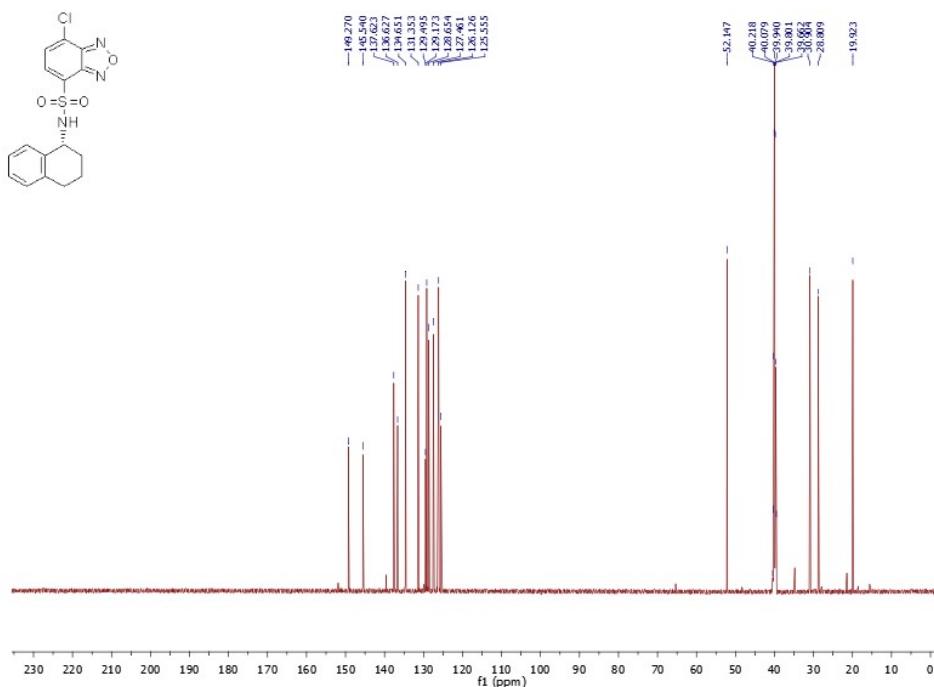
Compound 15b



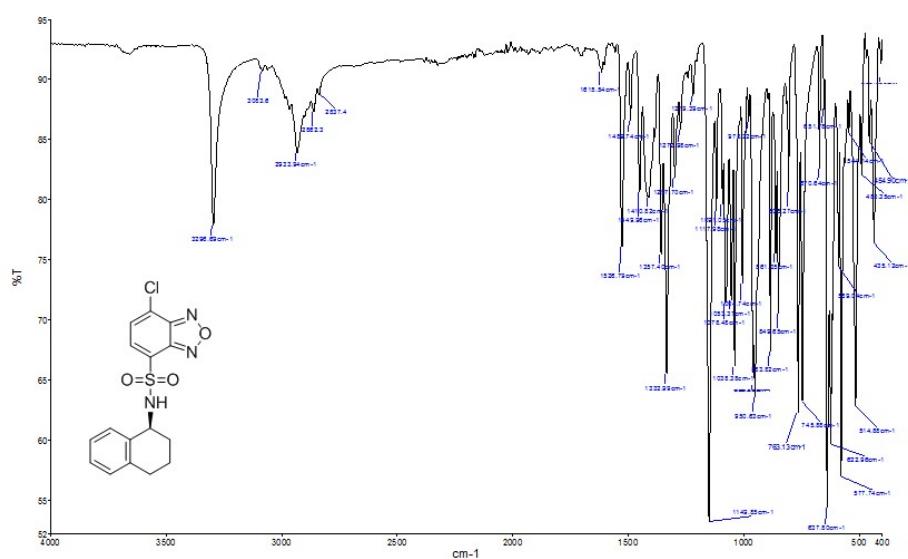


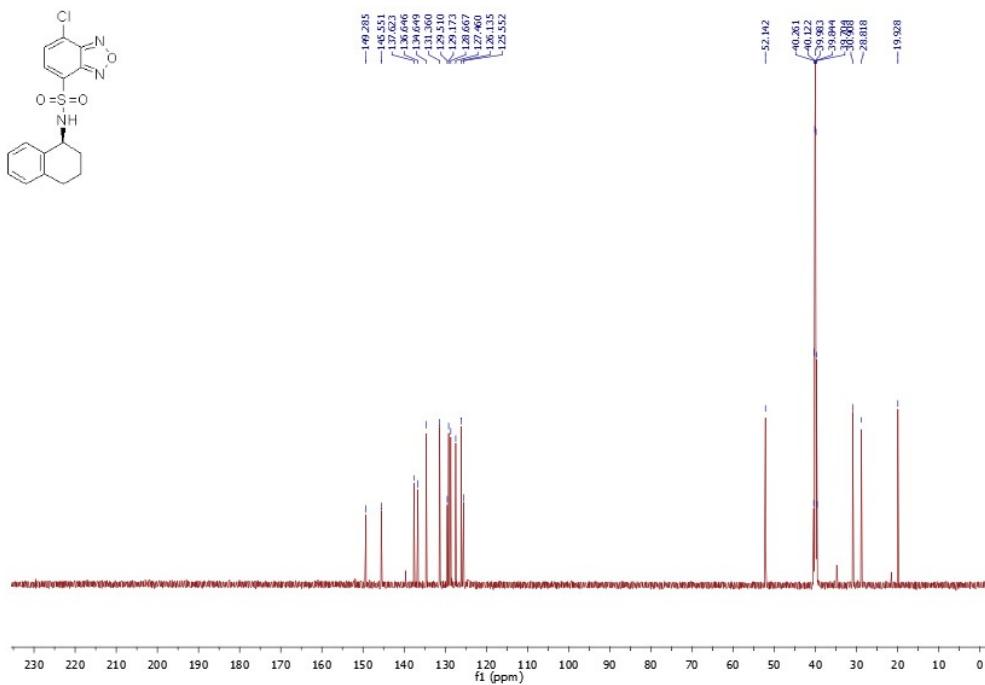
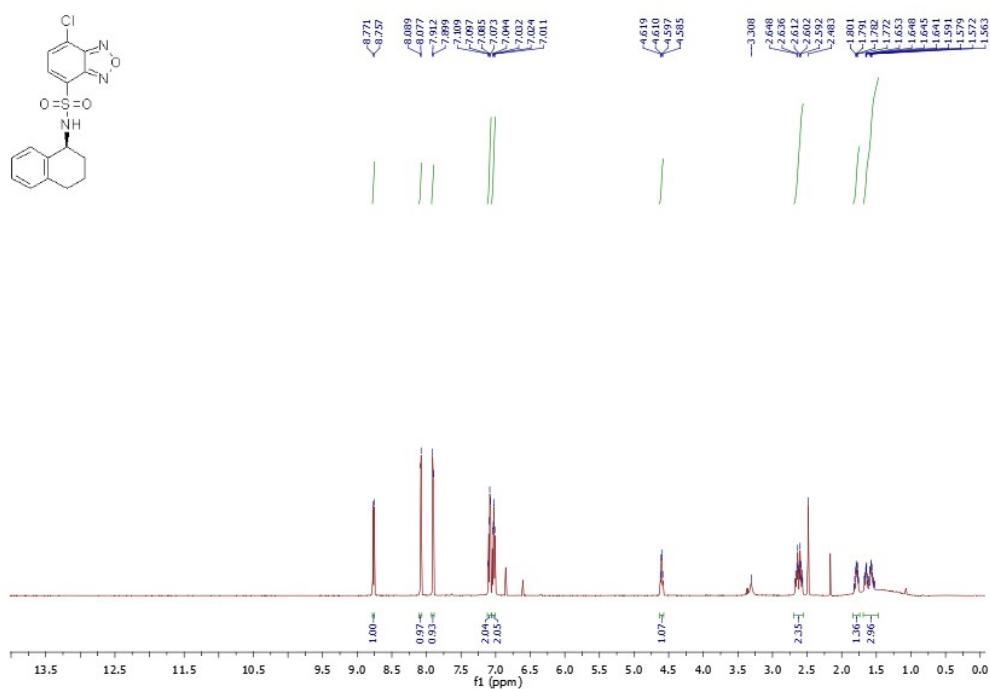
Compound 16a



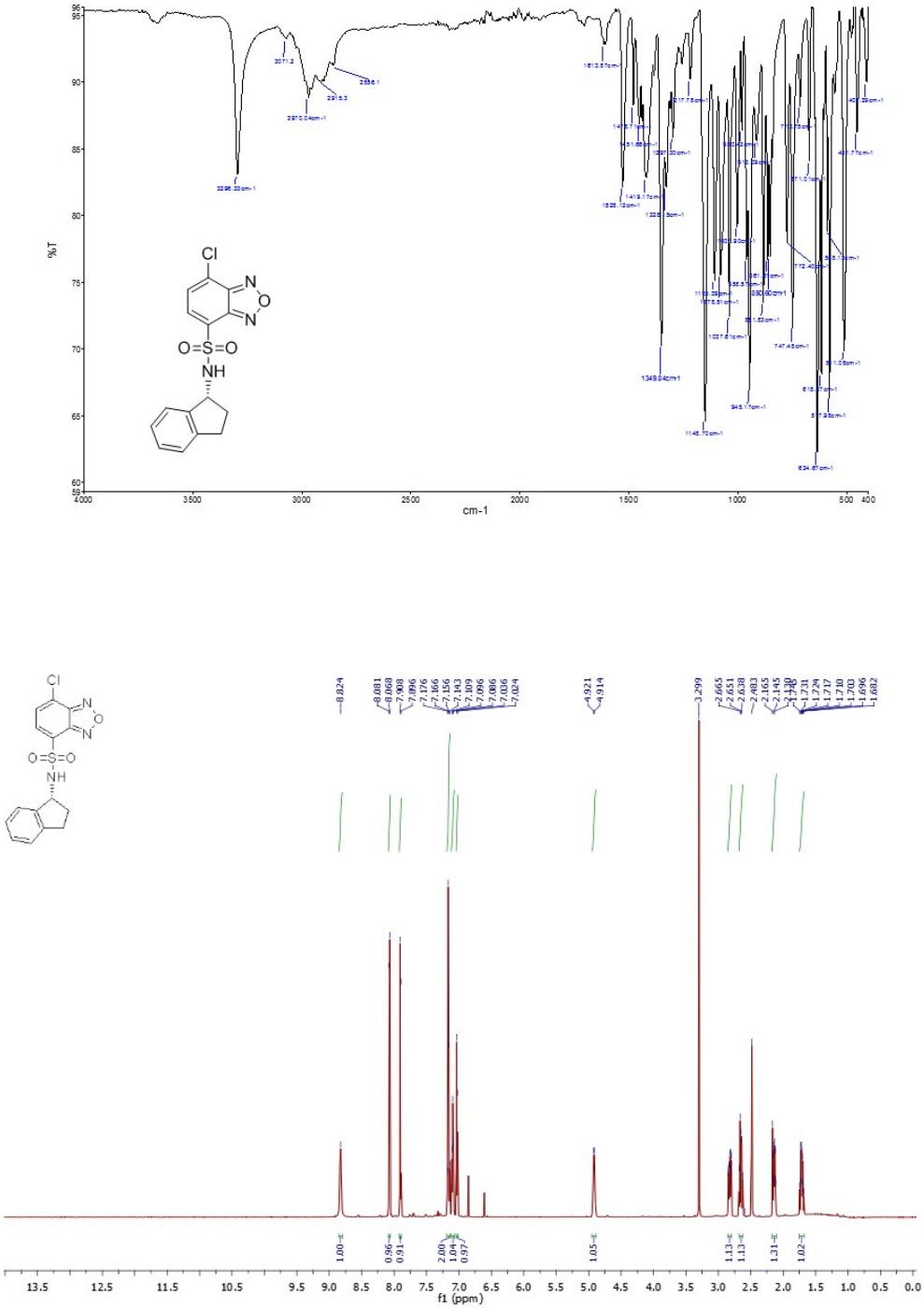


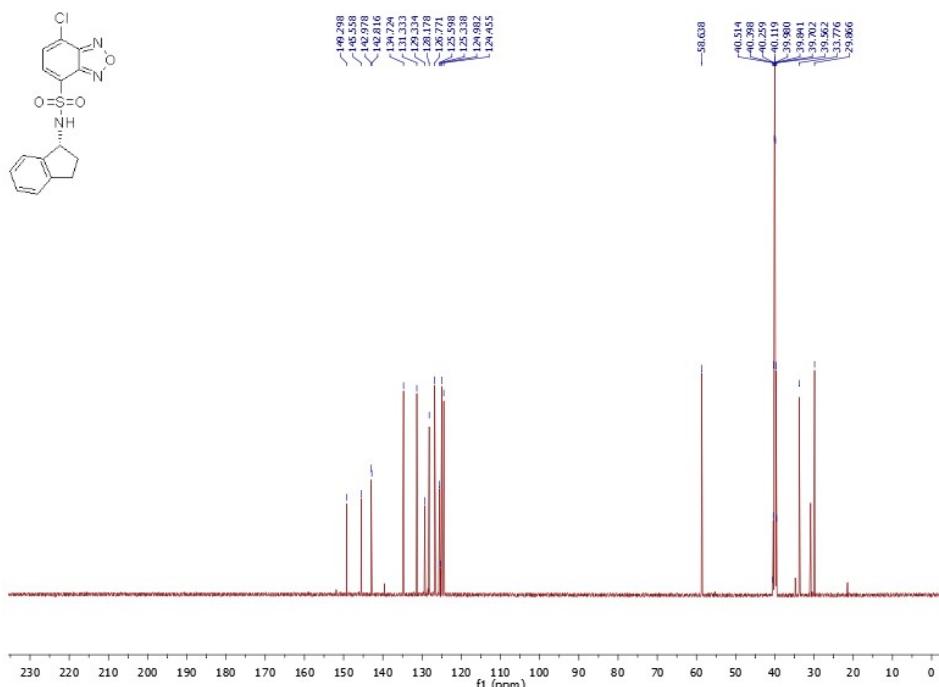
Compound 16b





Compound 17a





Compound 17b

