Electronic Supplementary Material (ESI) for RSC Advances.

Supplementary Materials

Synthesis of Potent and Selective HDAC6 Inhibitors led to Unexpected Opening of Quinazoline Ring

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Table S1: *Chemical fragments including the benzohydroxamate, 1,3-benzodioxole and quinazoline substructures, identified among HDAC6 inhibitors. The number of compounds including the fragments and their prevalence ("Actives / Inactives rate") among the active and inactive classes are reported in the table.*

Fragment ID	*Fragment SMILES*	*Global Rank*	*Number of HDAC6 compounds*	*Number of active compounds*	*Number of inactive compounds*	*Actives / Inactives rate*	*Substructure Class*
Fragment 1	O=Cc1ccc(C(=O)NO)cc1	6	42	41	1	41.00	benzohydroxamate
Fragment 2	NCc1ccc(C(=O)NO)cc1	44	402	382	20	19.10	benzohydroxamate
Fragment 3	Cc1ccc(C(=O)NO)cc1	97	508	470	38	12.37	benzohydroxamate
Fragment 4	CNc1ccc(C(=O)NO)cc1	145	93	83	10	8.30	benzohydroxamate
Fragment 5	O=C(NO)c1ccccc1	167	694	611	83	7.36	benzohydroxamate
Fragment 6	Nc1ccc(C(=O)NO)cc1	173	99	87	12	7.25	benzohydroxamate
Fragment 7	O=C(NO)c1ccc(Cl)cc1	177	8	7	1	7.00	benzohydroxamate
Fragment 8	Nc1cc(C(=O)NO)ccc1Cl	183	8	7	1	7.00	benzohydroxamate
Fragment 9	O=Cc1cccc(C(=O)NO)c1	213	7	6	1	6.00	benzohydroxamate
Fragment 10	CCc1ccc(C(=O)NO)cc1	287	92	76	16	4.75	benzohydroxamate
Fragment 11	NCc1cccc(C(=O)NO)c1	421	23	18	5	3.60	benzohydroxamate
Fragment 12	c1ccc2c(c1)OCO2	230	33	28	5	5.60	1,3 benzodixole
Fragment 13	CCc1ccc2c(c1)OCO2	235	26	22	4	5.50	1,3 benzodixole
Fragment 14	Cc1ccc2c(c1)OCO2	238	32	27	5	5.40	1,3 benzodixole
Fragment 15	Cc1ncc2ccccc2n1	141	70	63	7	9.00	quinazoline
Fragment 16	c1ccc2ncncc2c1	491	151	115	36	3.19	quinazoline
Fragment 17	Cc1ncnc2ccccc12	509	4	3	1	3.00	quinazoline

Table S2: *Top-ranking similarities obtained for the derivatives 11a and 11b with respect to the HDAC6 ligands reported in ChEMBL, according to the MACCS and ECFP4 fingerprints. The similarity degree between the ligands is reported as a mean of the Tanimoto index. Only similarity values above commonly accepted thresholds are reported. The document reference ID of the ligands in ChEMBL are also reported.*

Compound ID	*ChEMBL ID*	*MACCSfp similarity score*	*ECFP4fp similarity score*	*Document ChEMBL ID*
11a	CHEMBL3655929	0.844	0.5	CHEMBL3639071
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11a	CHEMBL4073021	0.633	0.606	CHEMBL4024792
11a	CHEMBL3314863	0.683	0.6	CHEMBL3351281
11a	CHEMBL3601776	0.734	0.564	CHEMBL3600352
11a	CHEMBL3918660	0.646	0.556	CHEMBL3886619
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11a	CHEMBL3893799	0.6	0.556	CHEMBL3886619
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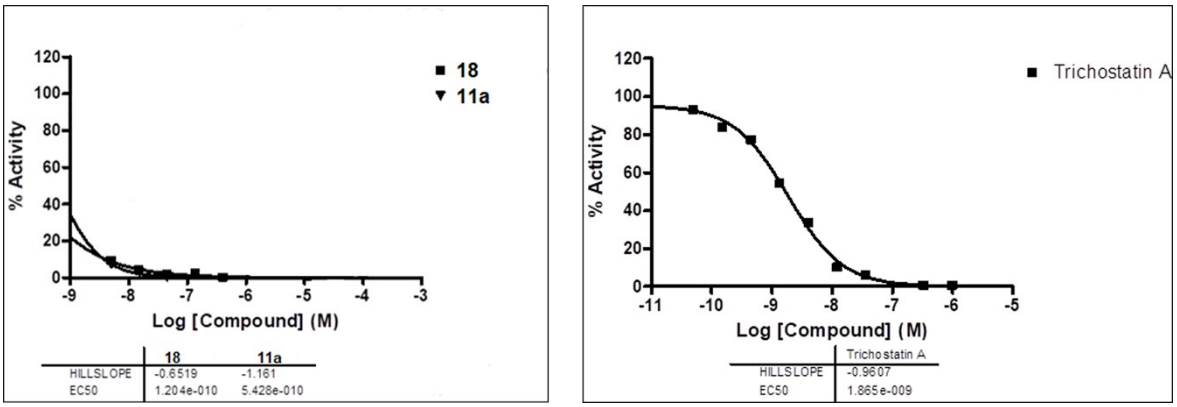


Figure S1. Dose response curves of **11a** and **18** tested against **HDAC6**. All compounds were tested in singlet 10-dose IC_{50} mode with 3-fold serial dilution starting at 100 µM**.** HDAC reference compound Trichostatin A (TSA) was tested in a 10-dose IC_{50} with 3-fold serial dilution starting at 1 µM. IC_{50} values were calculated using the GraphPad Prism4 program based on a sigmoidal dose-response equation.

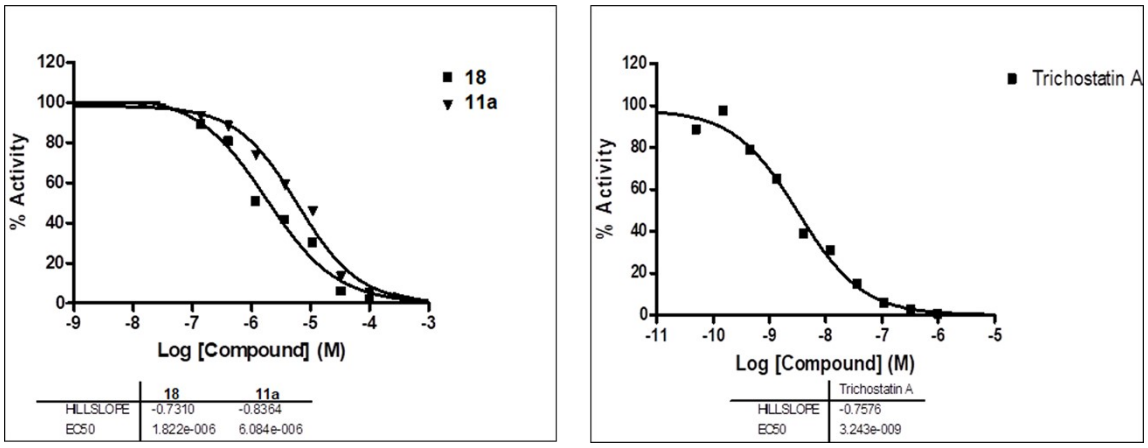


Figure S2. Dose response curves of **11a** and **18** tested against **HDAC1**. All compounds were tested in singlet 10-dose IC_{50} mode with 3-fold serial dilution starting at 100 µM. HDAC reference compound Trichostatin A (TSA) was tested in a 10-dose IC_{50} with 3-fold serial dilution starting at 1 µM. IC_{50} values were calculated using the GraphPad Prism4 program based on a sigmoidal dose-response equation.

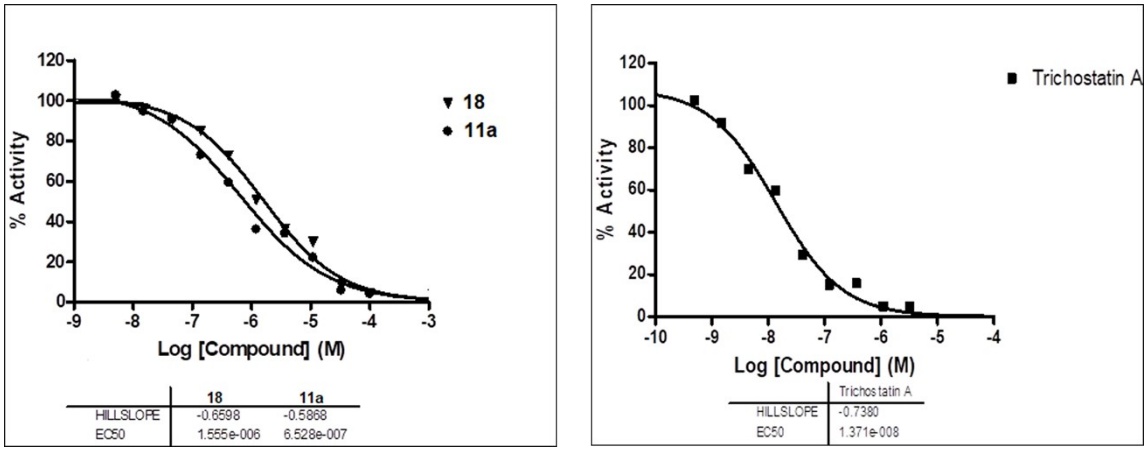
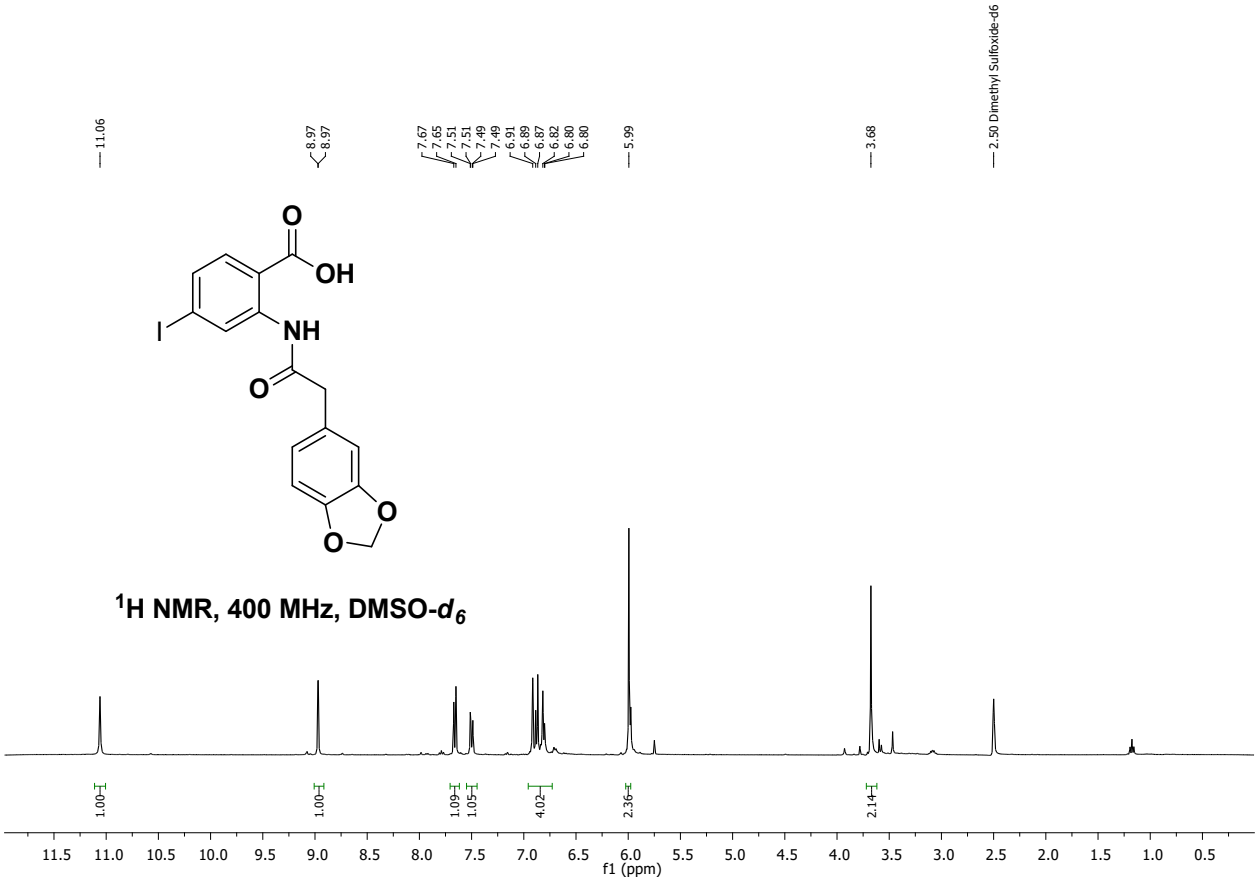


Figure S3. Dose response curves of **11a** and **18** tested against **HDAC8**. All compounds were tested in singlet 10-dose IC_{50} mode with 3-fold serial dilution starting at 100 µM. HDAC reference compound Trichostatin A (TSA) was tested in a 10-dose IC_{50} with 3-fold serial dilution starting at 1 µM. IC_{50} values were calculated using the GraphPad Prism4 program based on a sigmoidal dose-response equation.

^{1}H, ^{13}C NMR Spectra for all compounds



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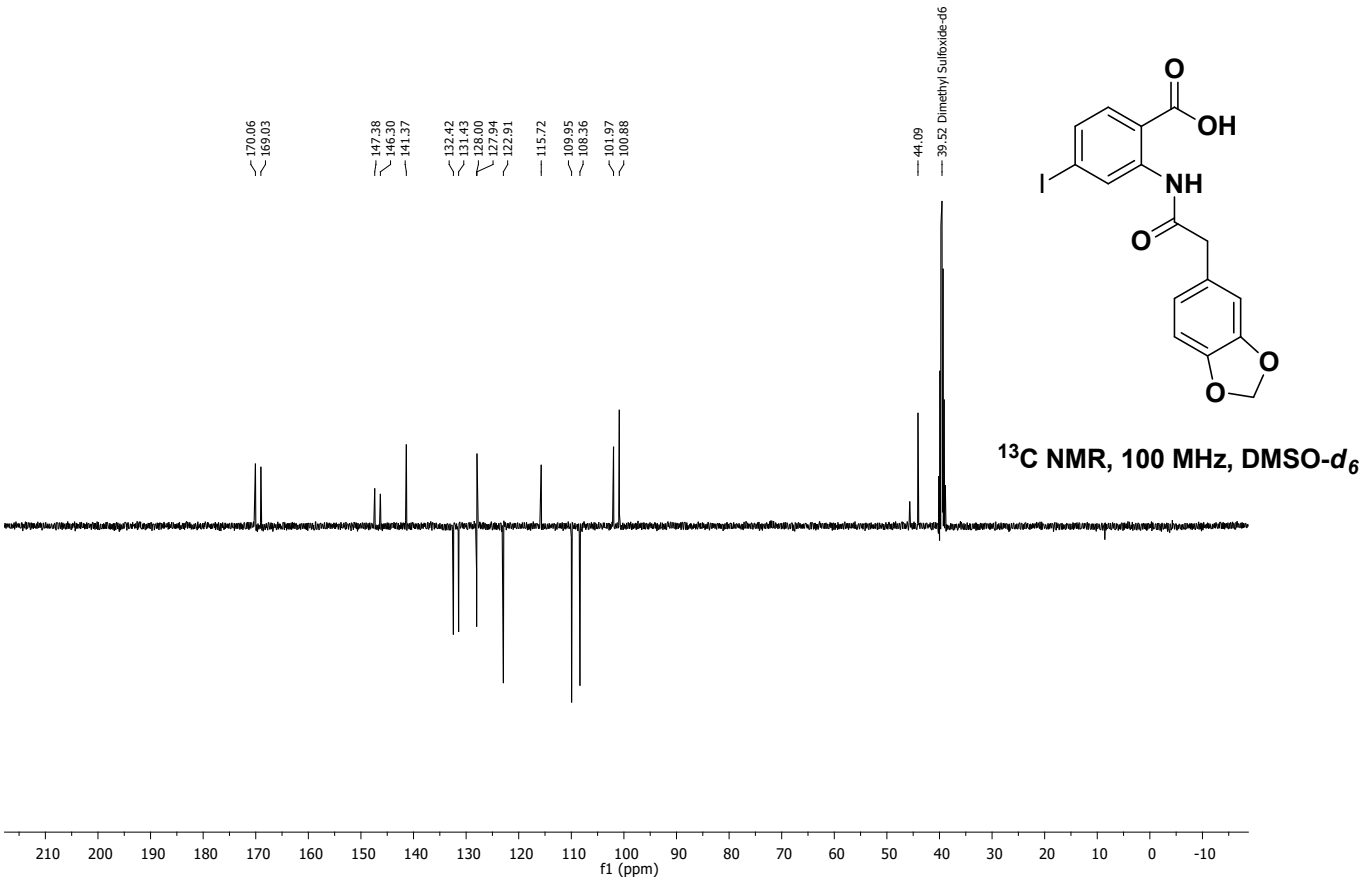

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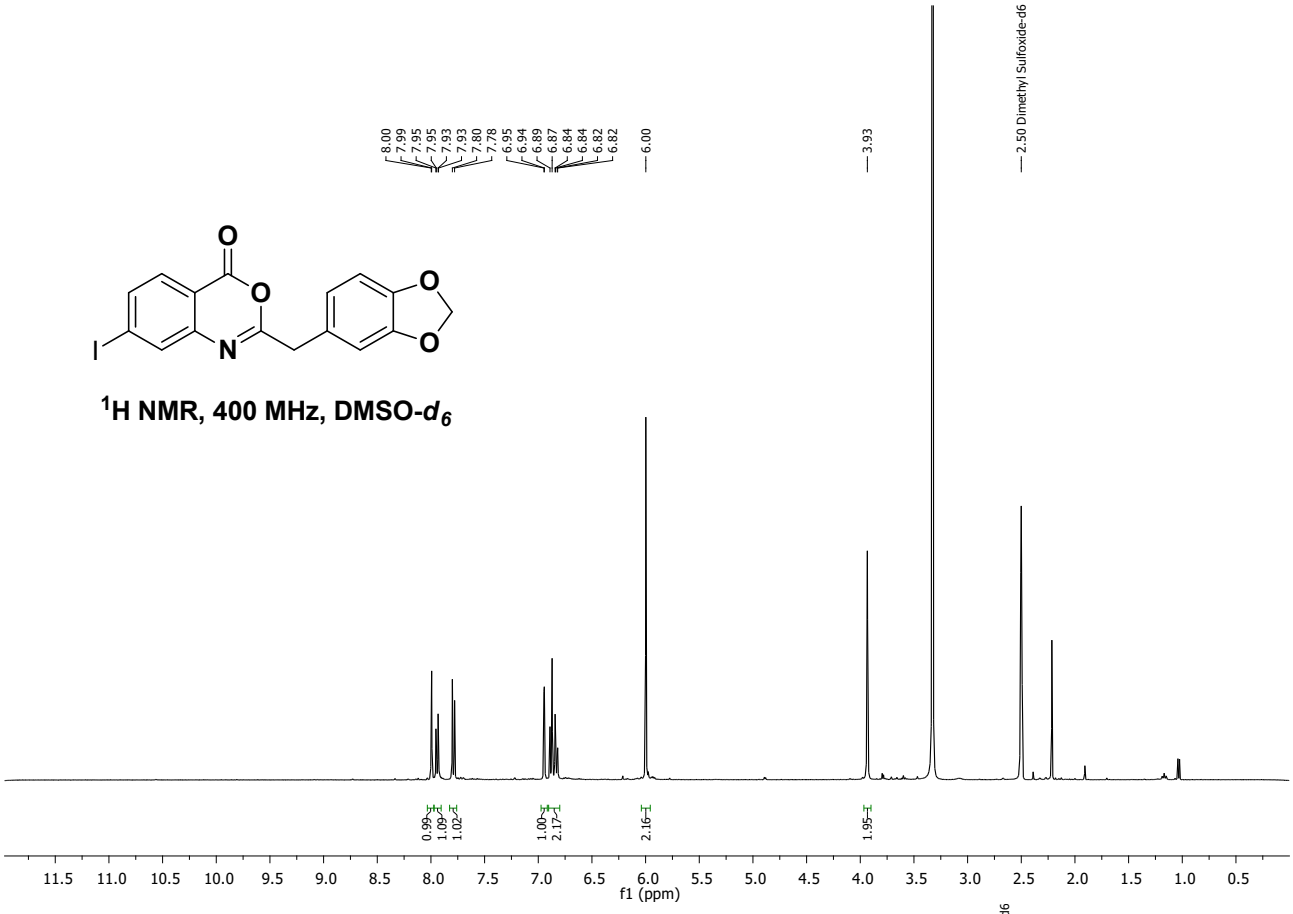

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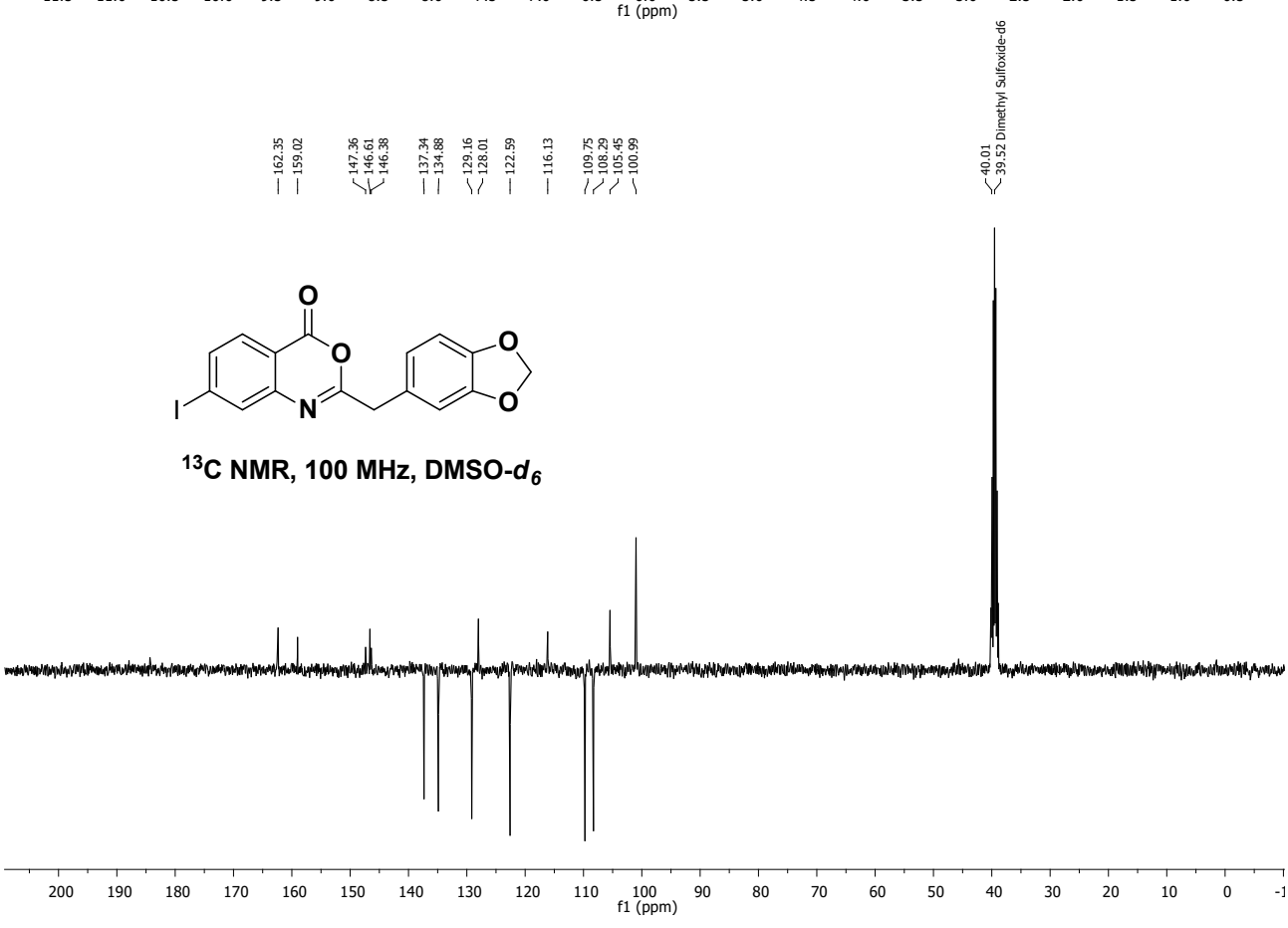

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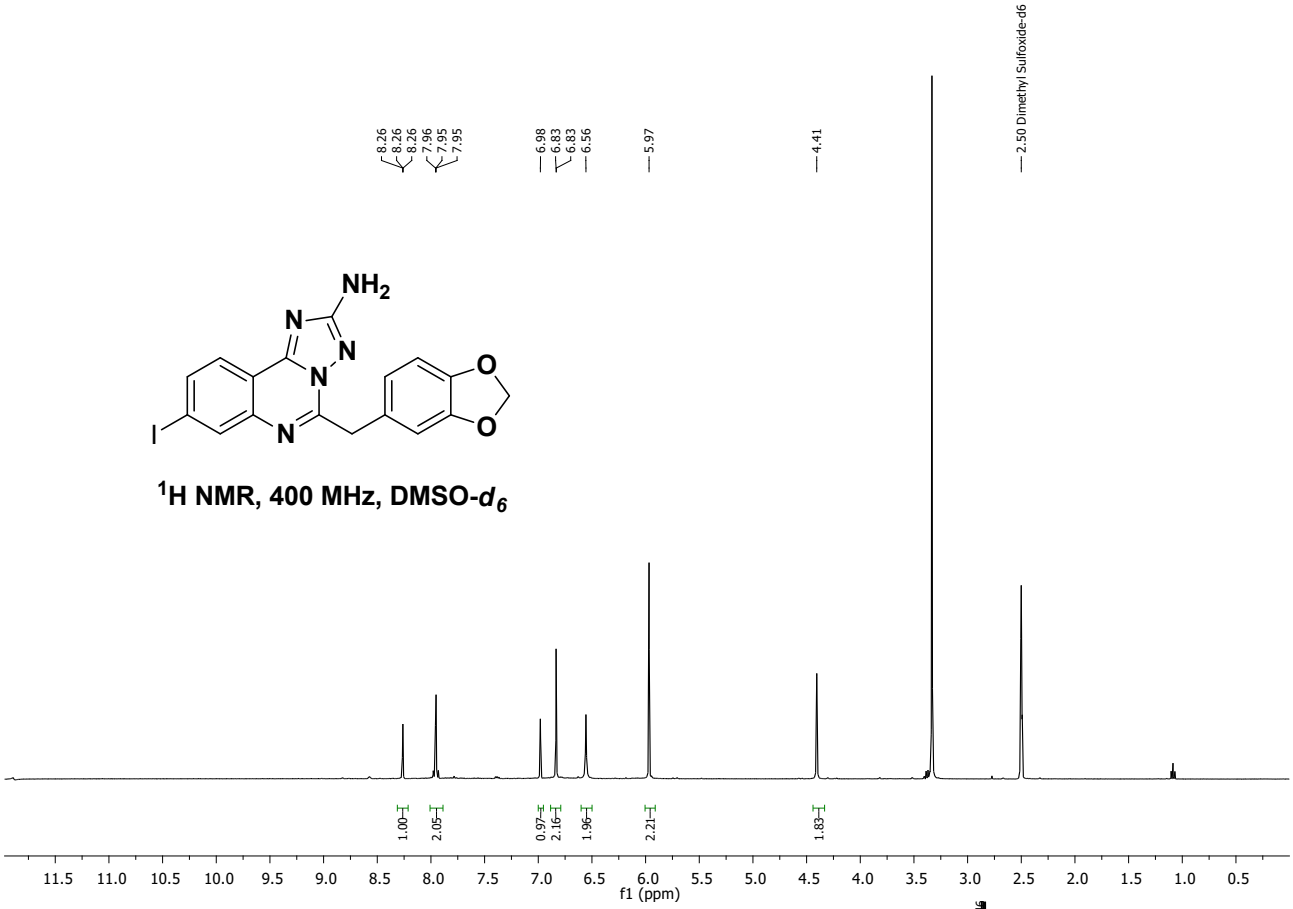

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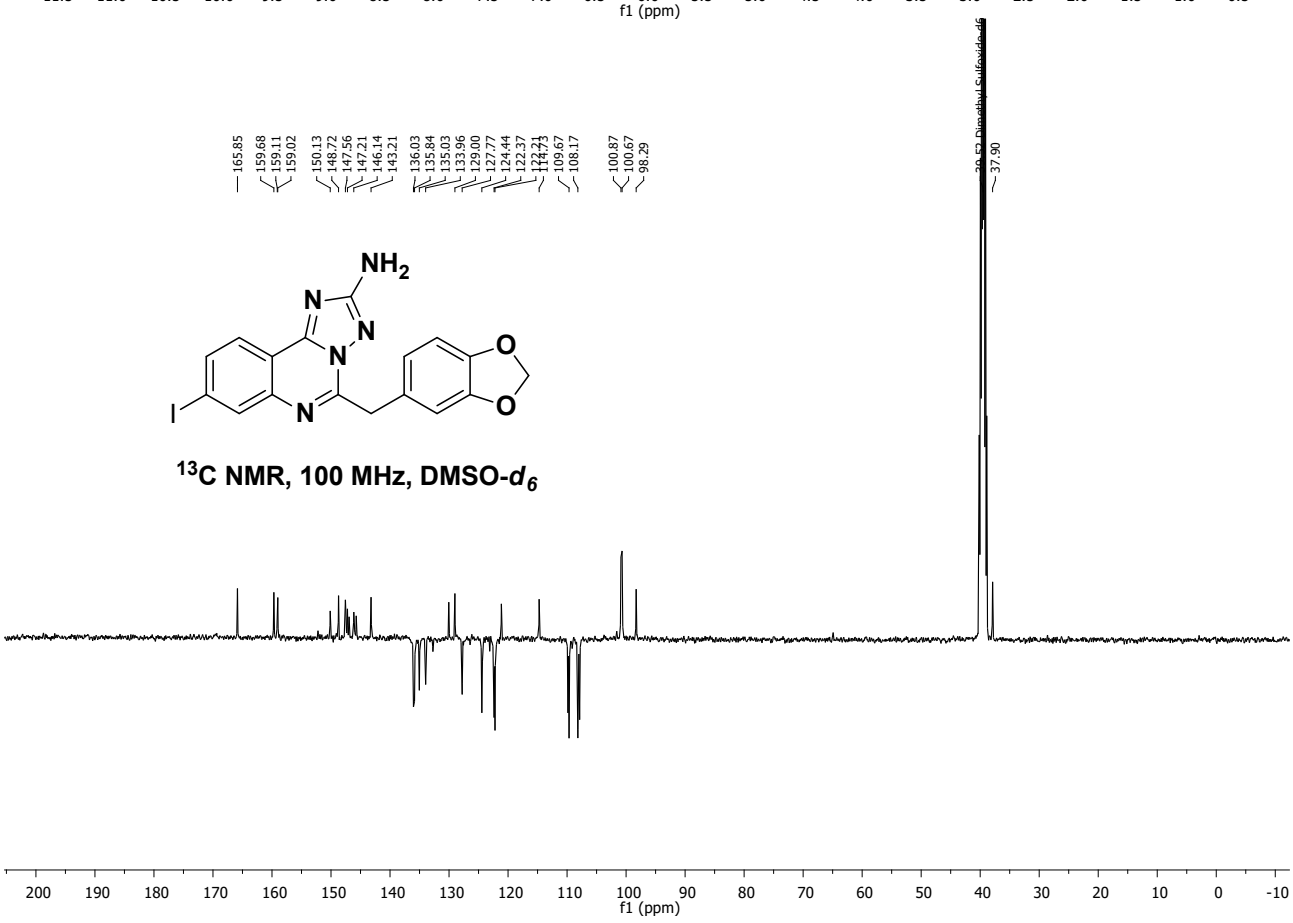
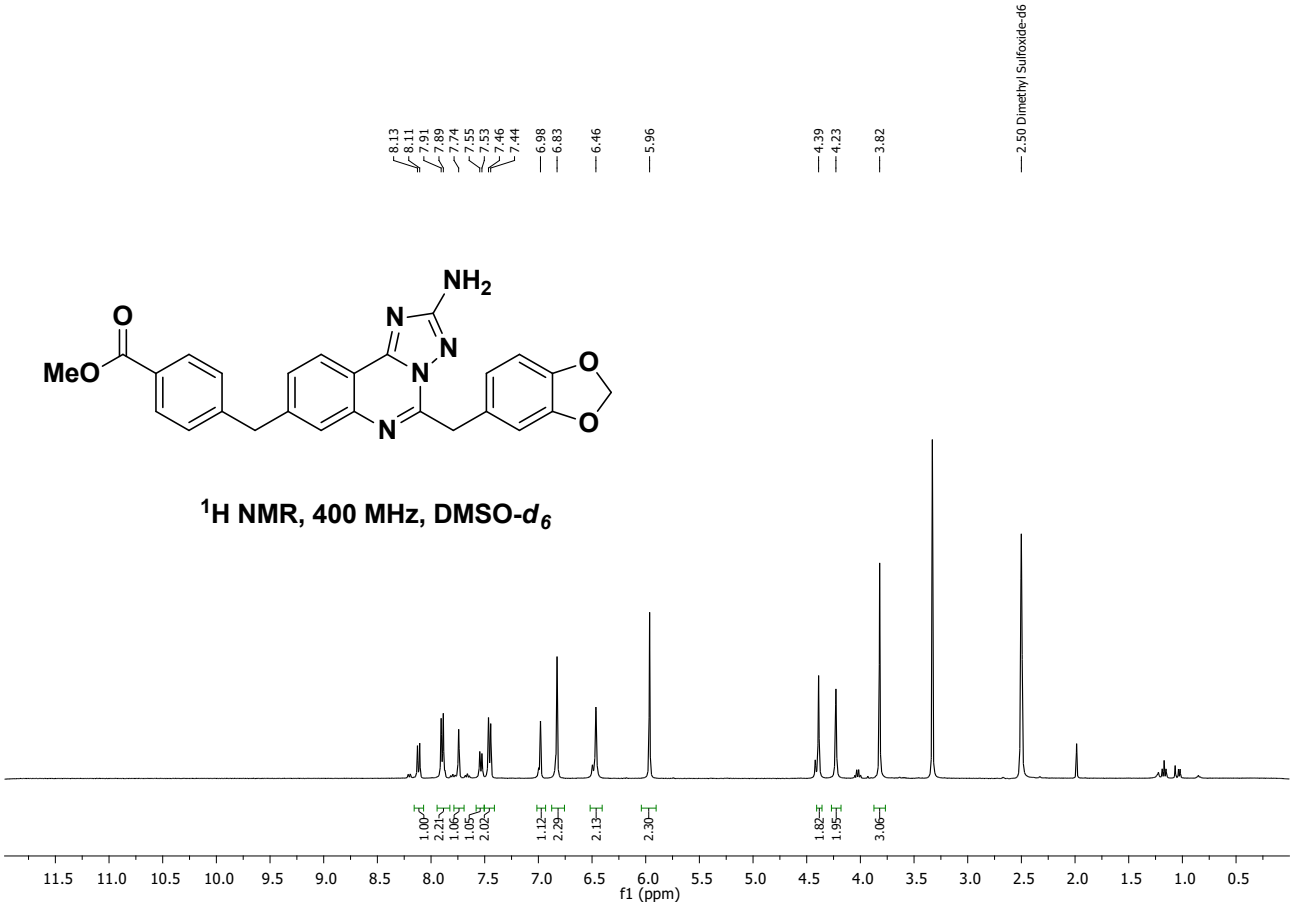
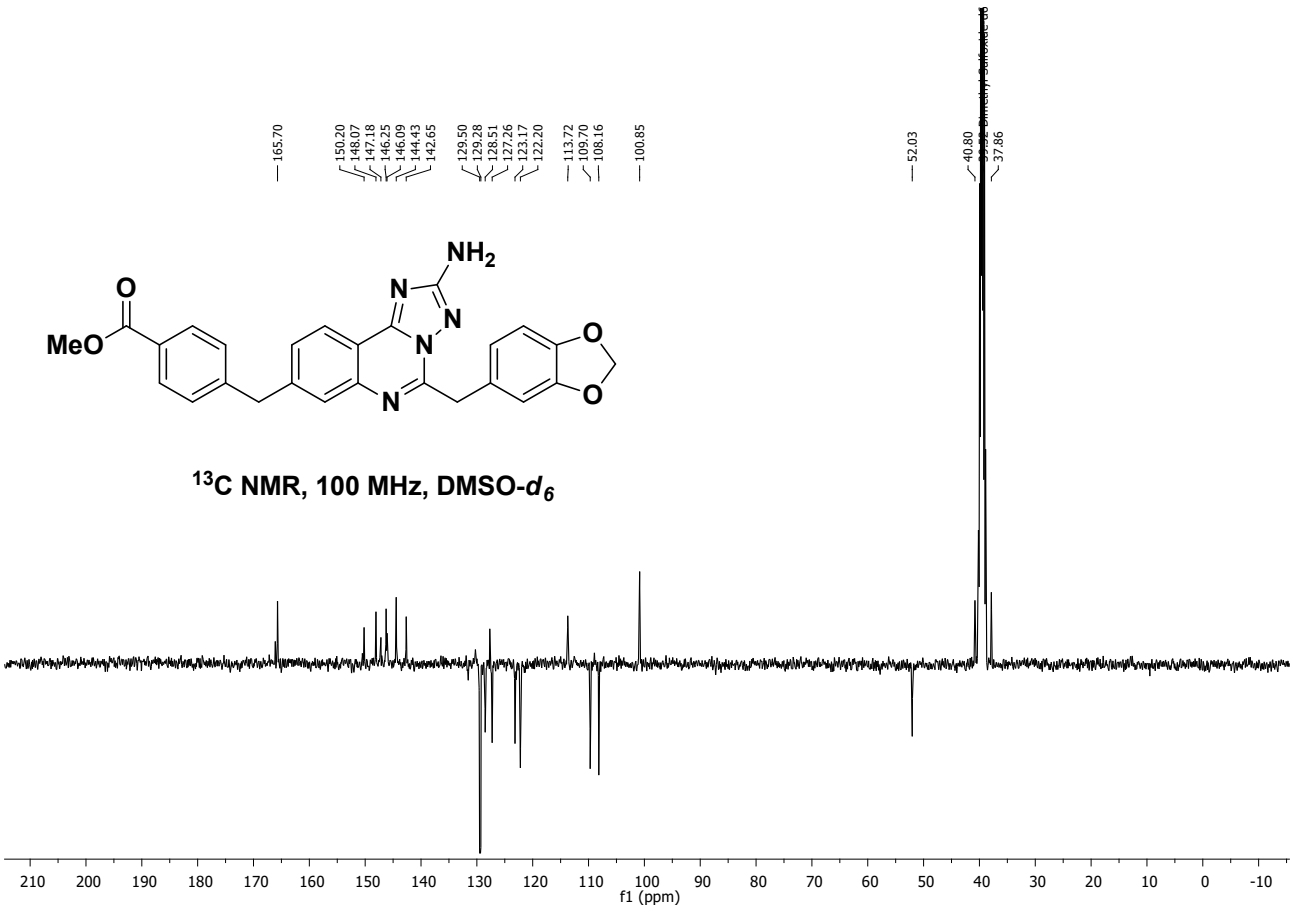


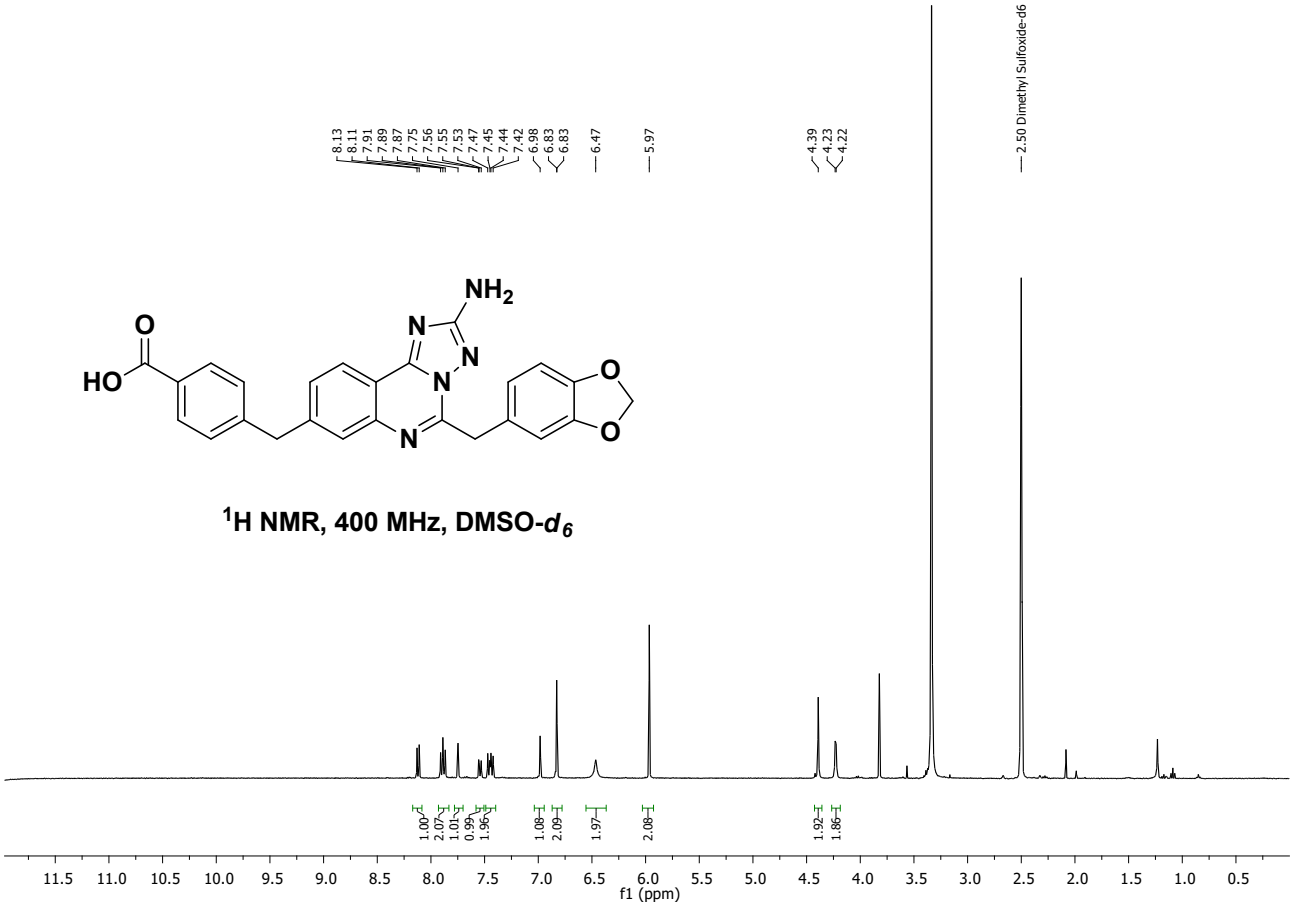
^{13}C NMR, 100 MHz, DMSO-*d*$_6$



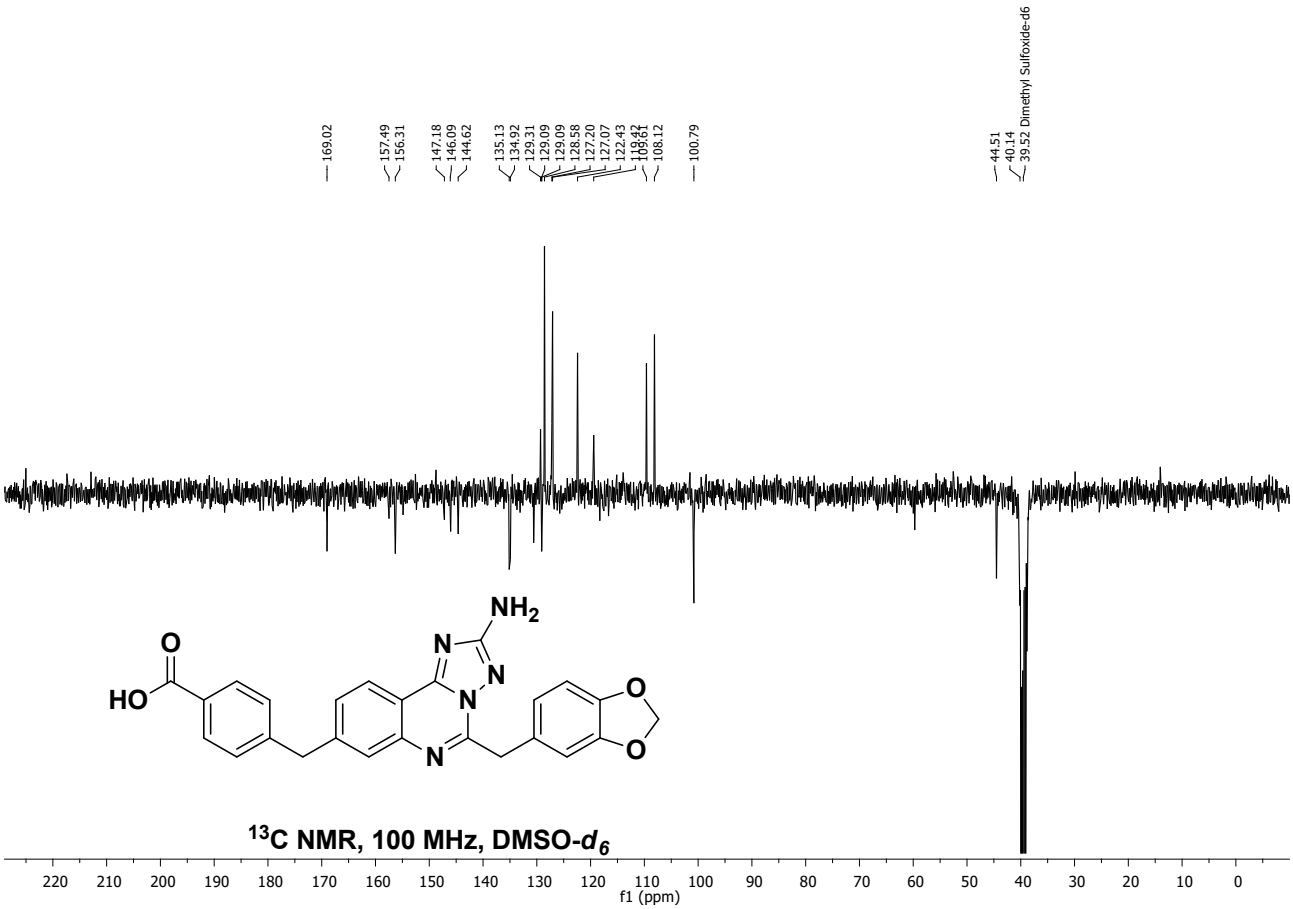
^{1}H NMR, 400 MHz, DMSO-*d*$_6$



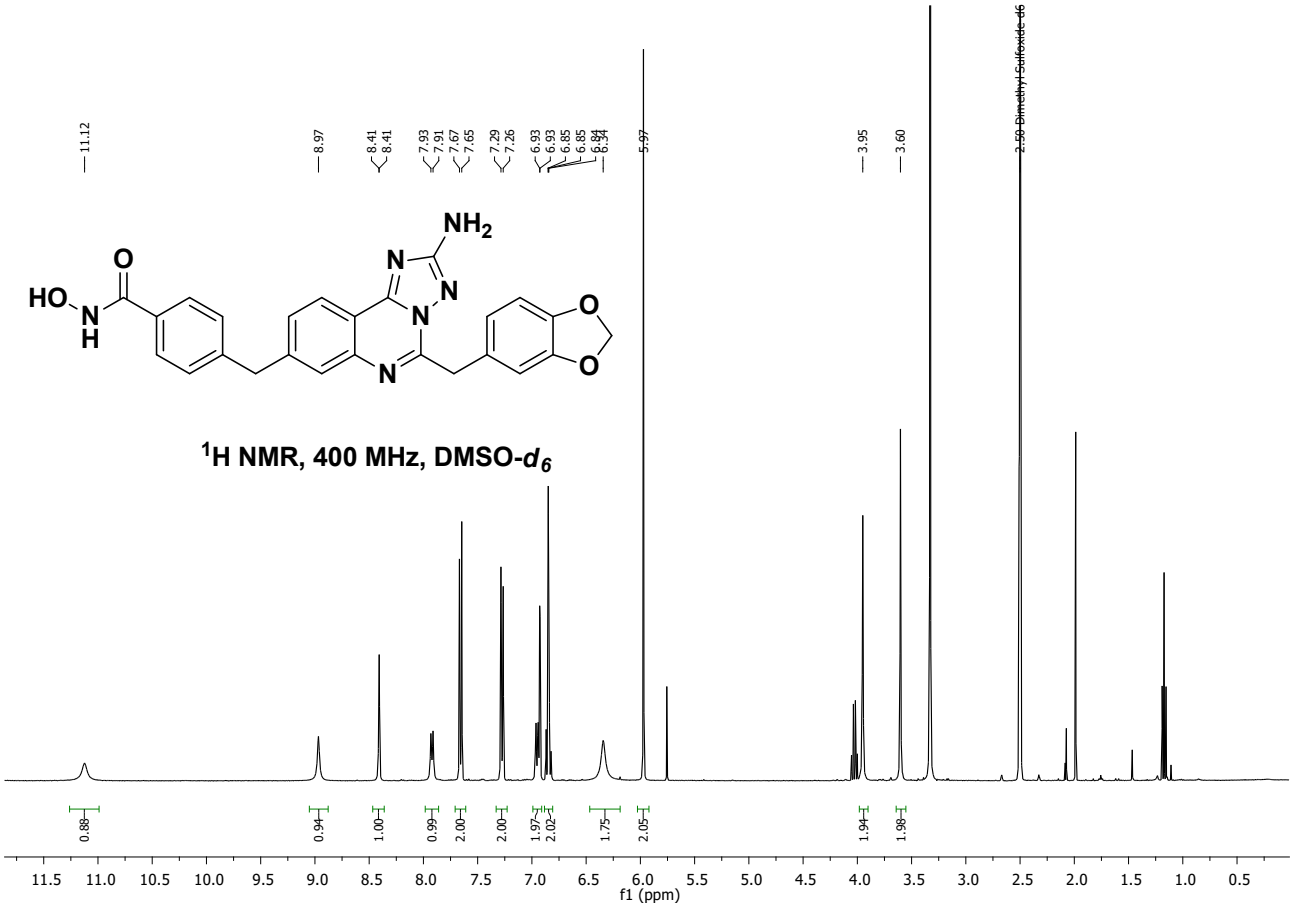
^{13}C NMR, 100 MHz, DMSO-*d*$_6$



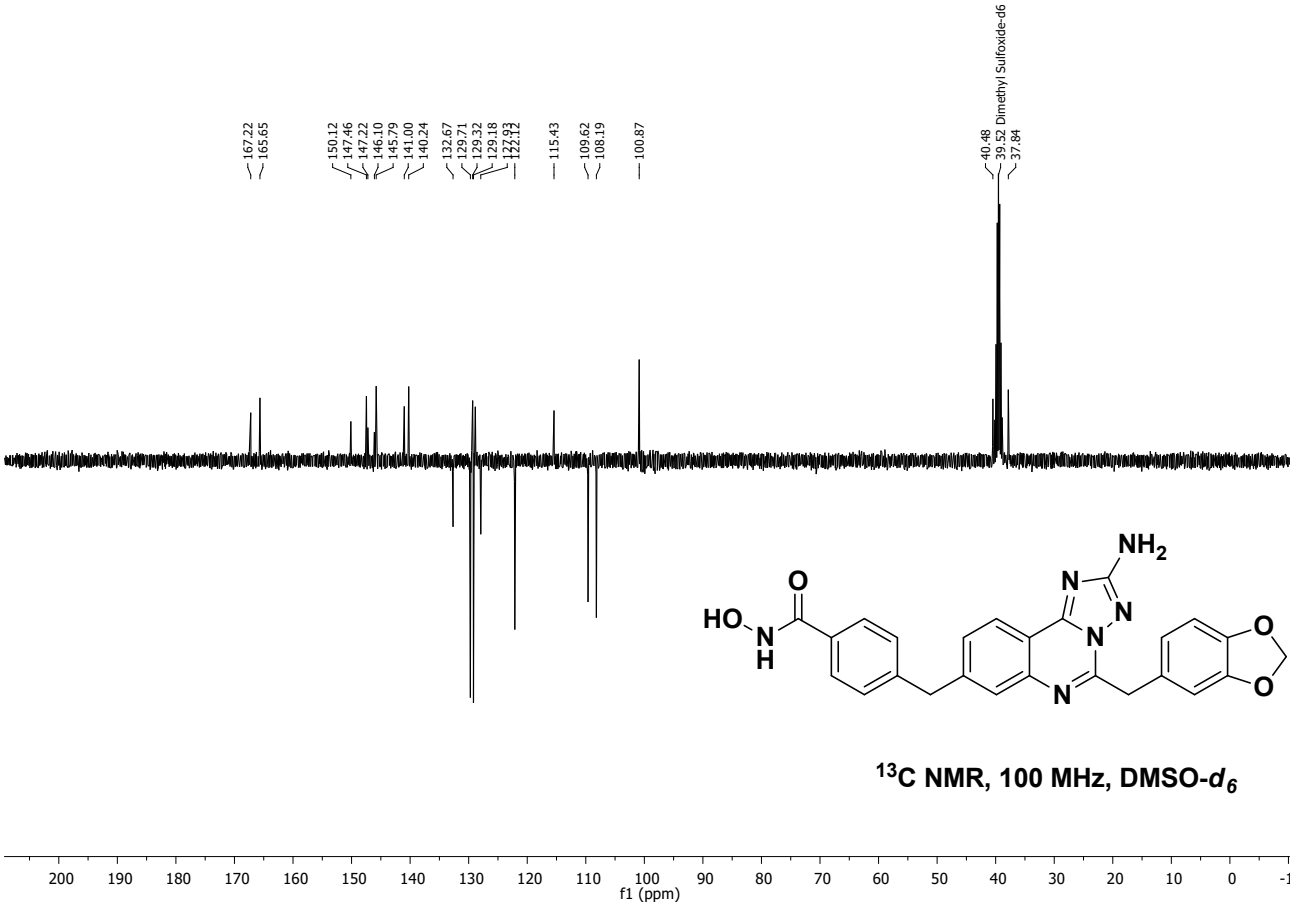
^{1}H NMR, 400 MHz, DMSO-*d*$_6$



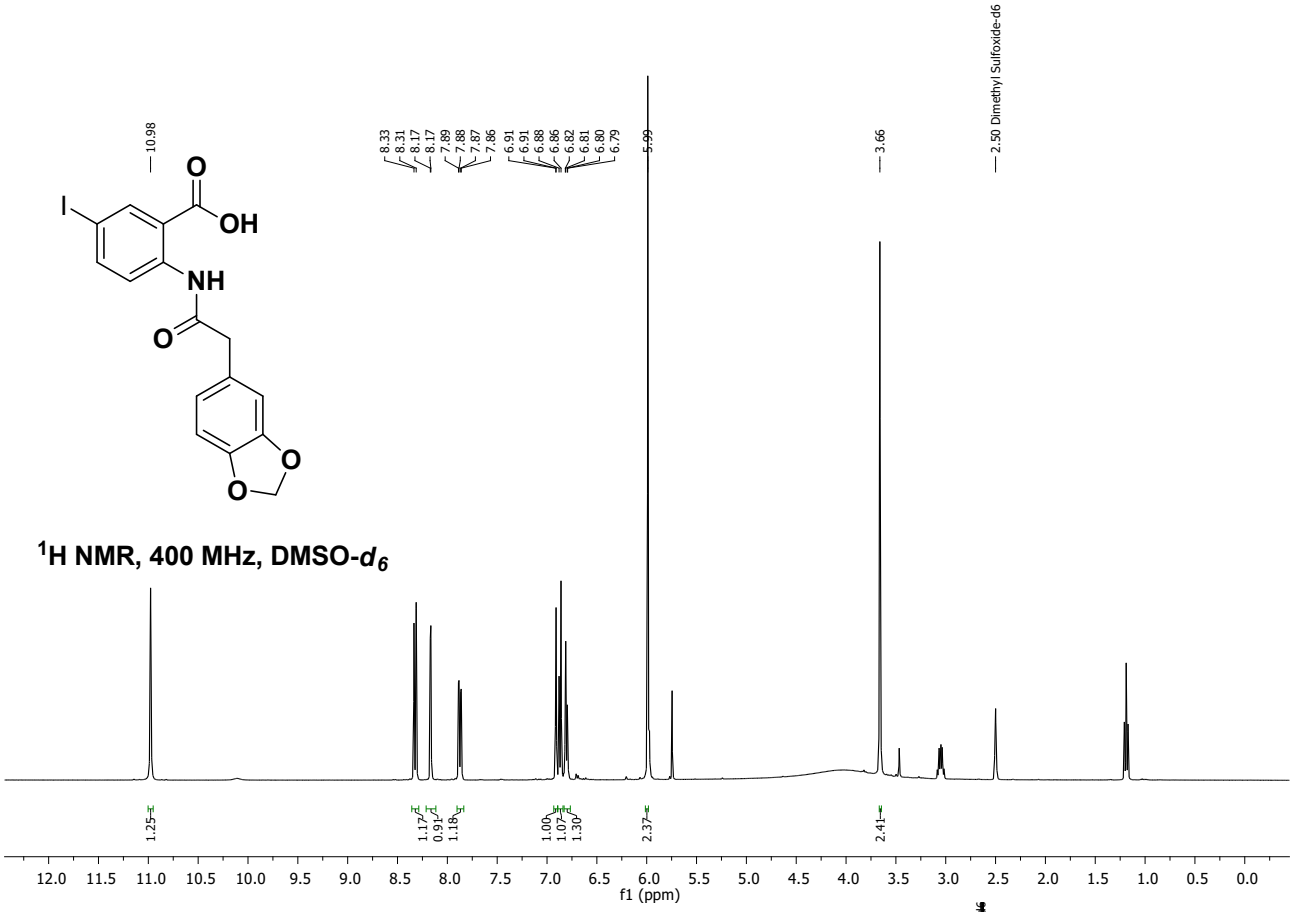
^{13}C NMR, 100 MHz, DMSO-*d*$_6$



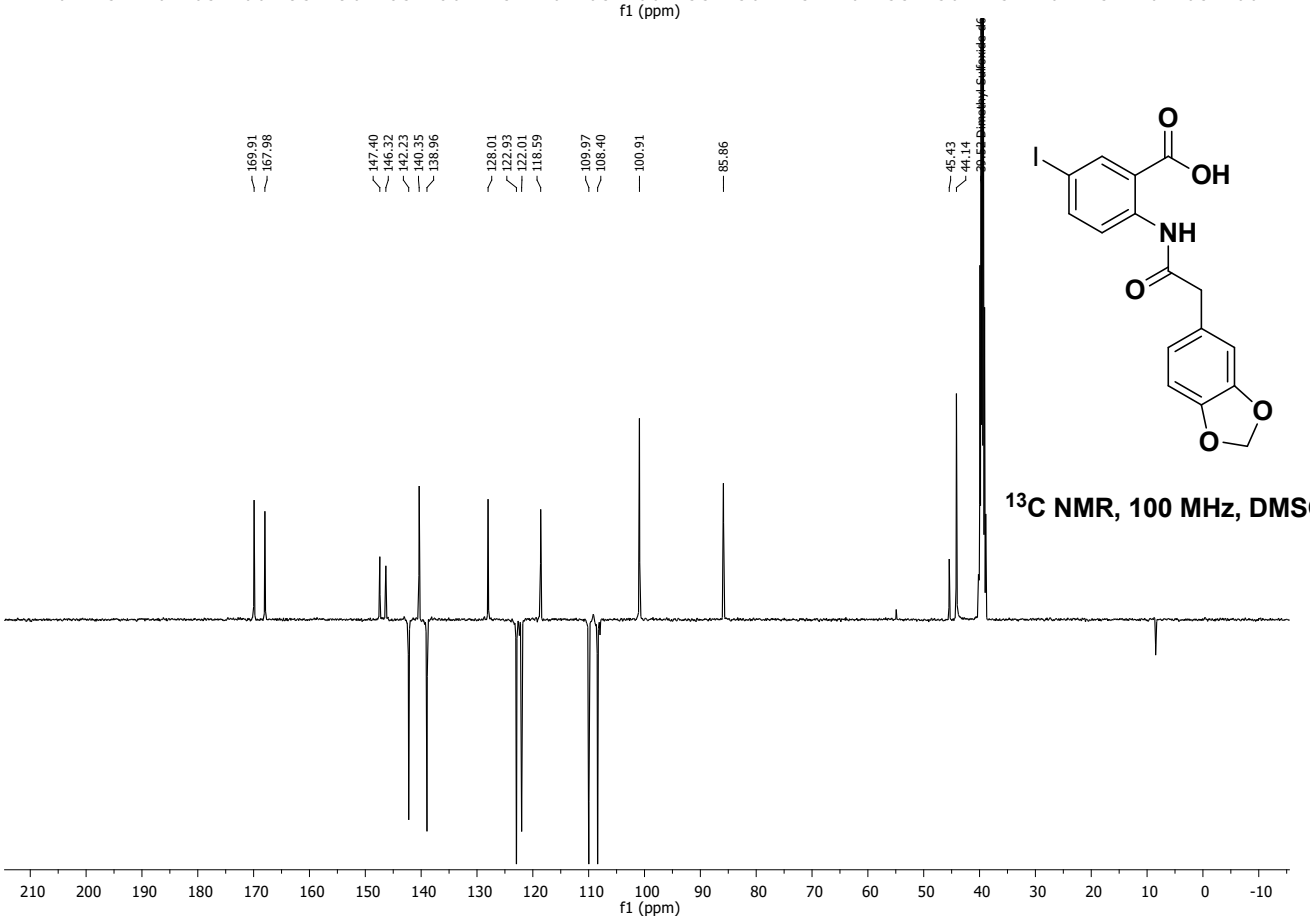
^{1}H NMR, 400 MHz, DMSO-*d*$_6$



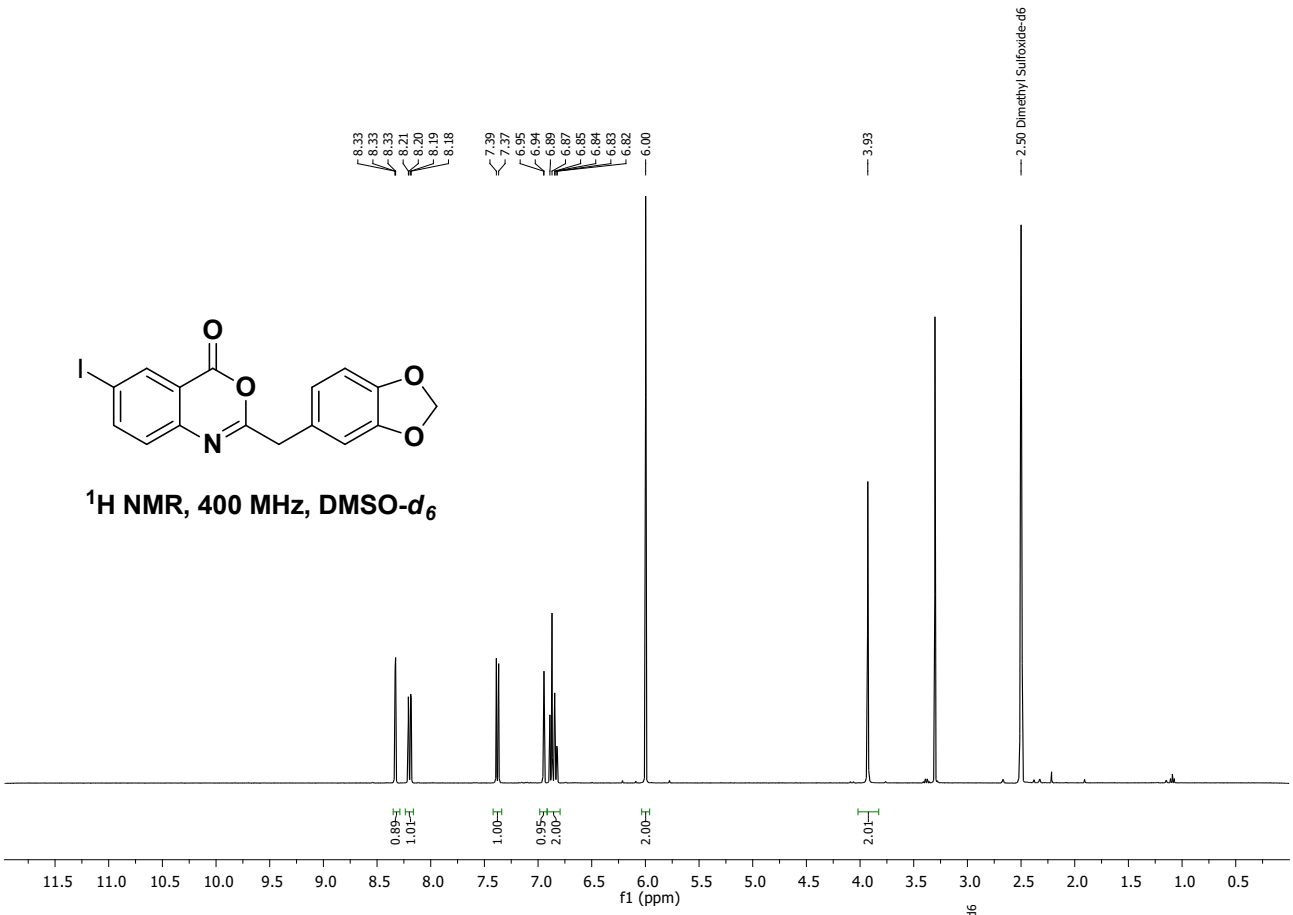
^{13}C NMR, 100 MHz, DMSO-*d*$_6$



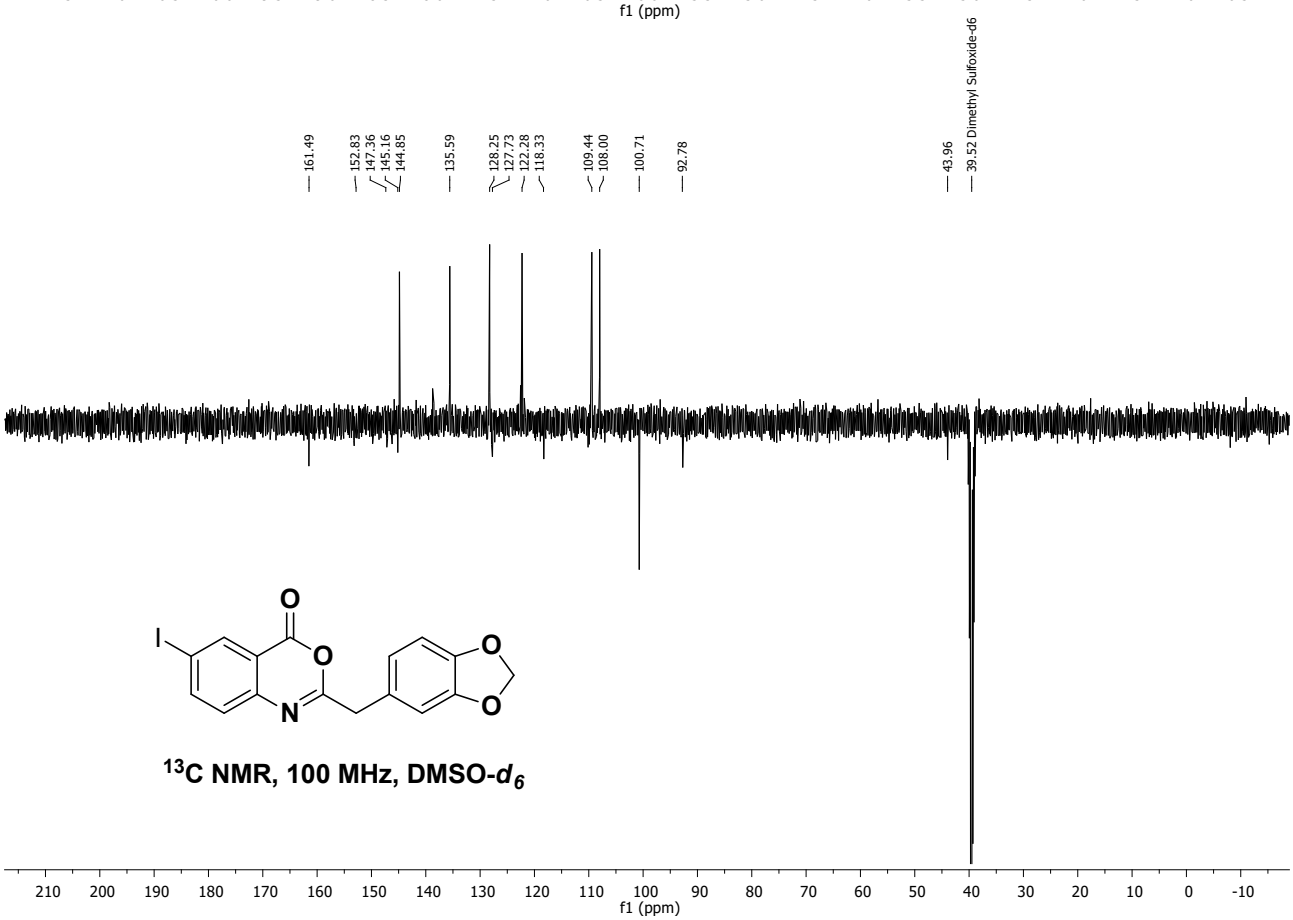
^{1}H NMR, 400 MHz, DMSO-*d*$_6$



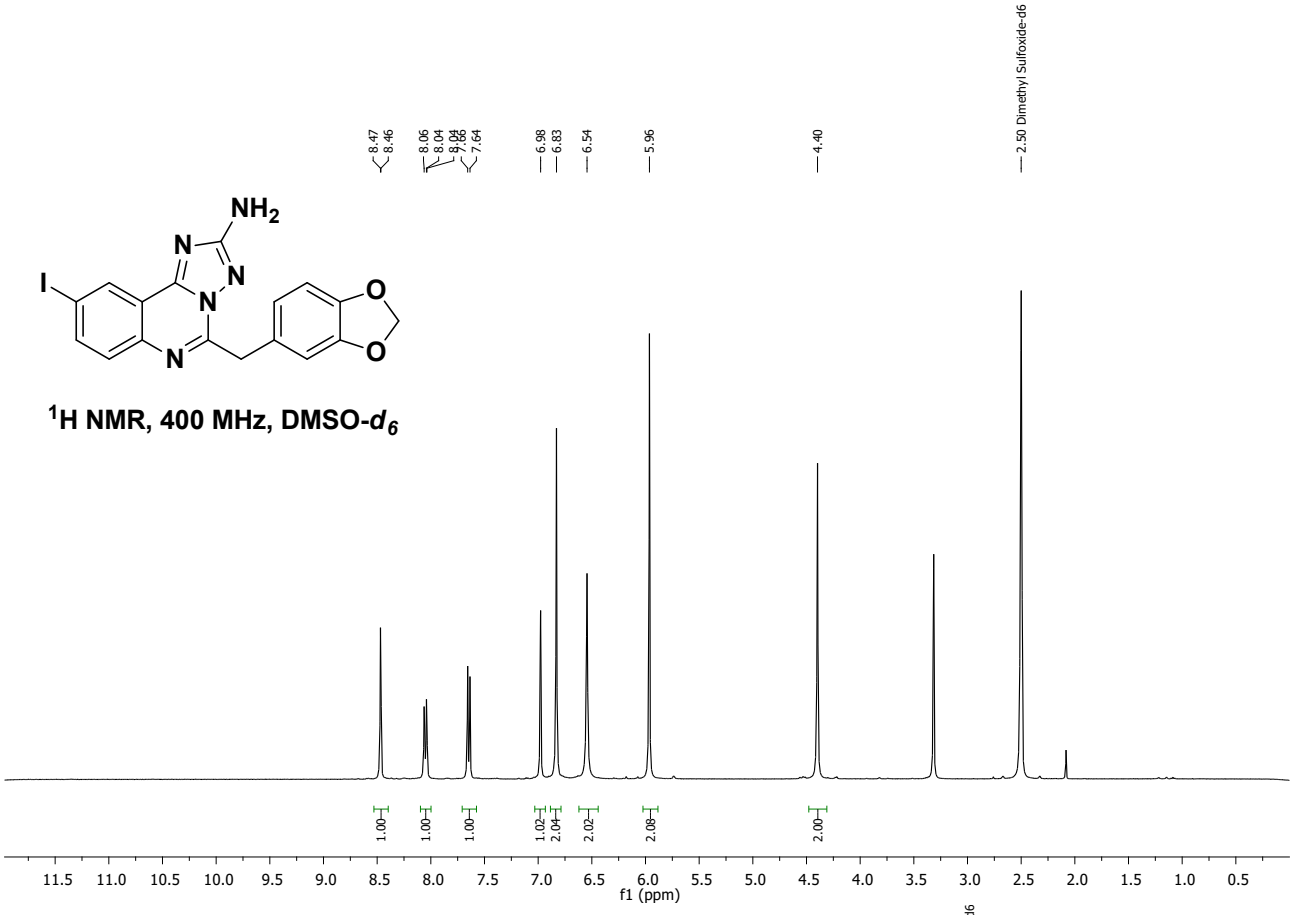
^{13}C NMR, 100 MHz, DMSO-*d*$_6$



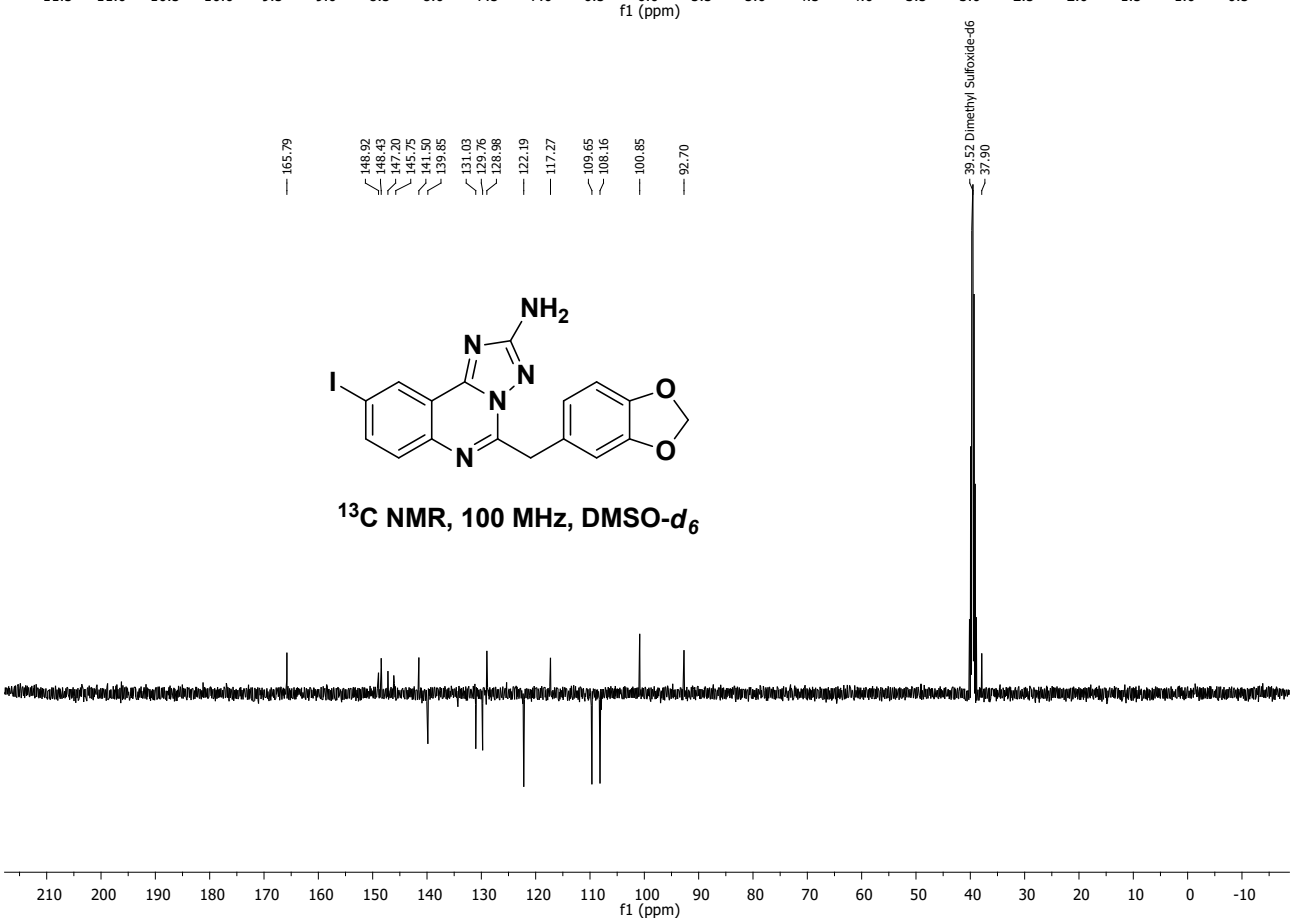
^{1}H NMR, 400 MHz, DMSO-*d*$_6$



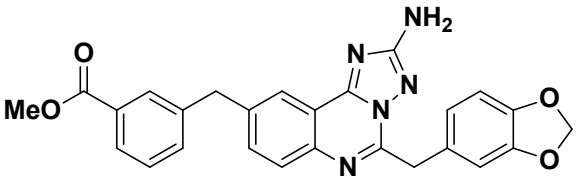
^{13}C NMR, 100 MHz, DMSO-*d*$_6$



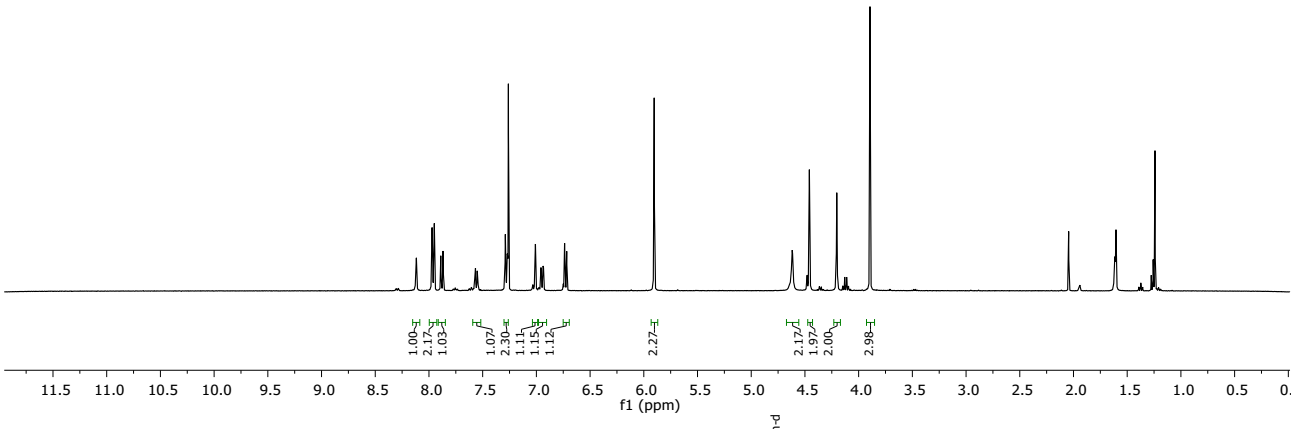
^{1}H NMR, 400 MHz, DMSO-*d*$_6$

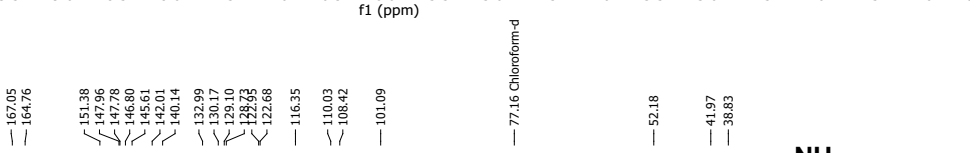


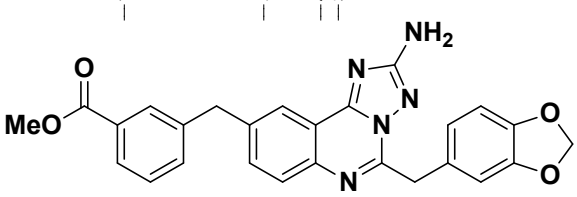
^{13}C NMR, 100 MHz, DMSO-*d*$_6$



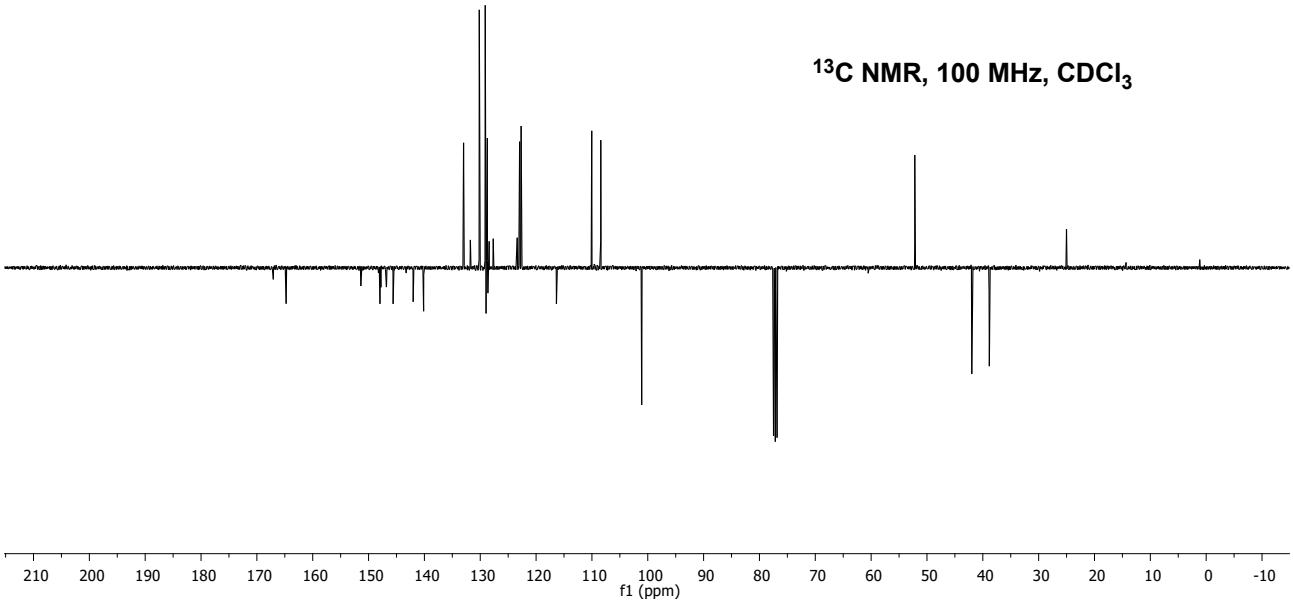
^{1}H NMR, 400 MHz, $CDCl_3$

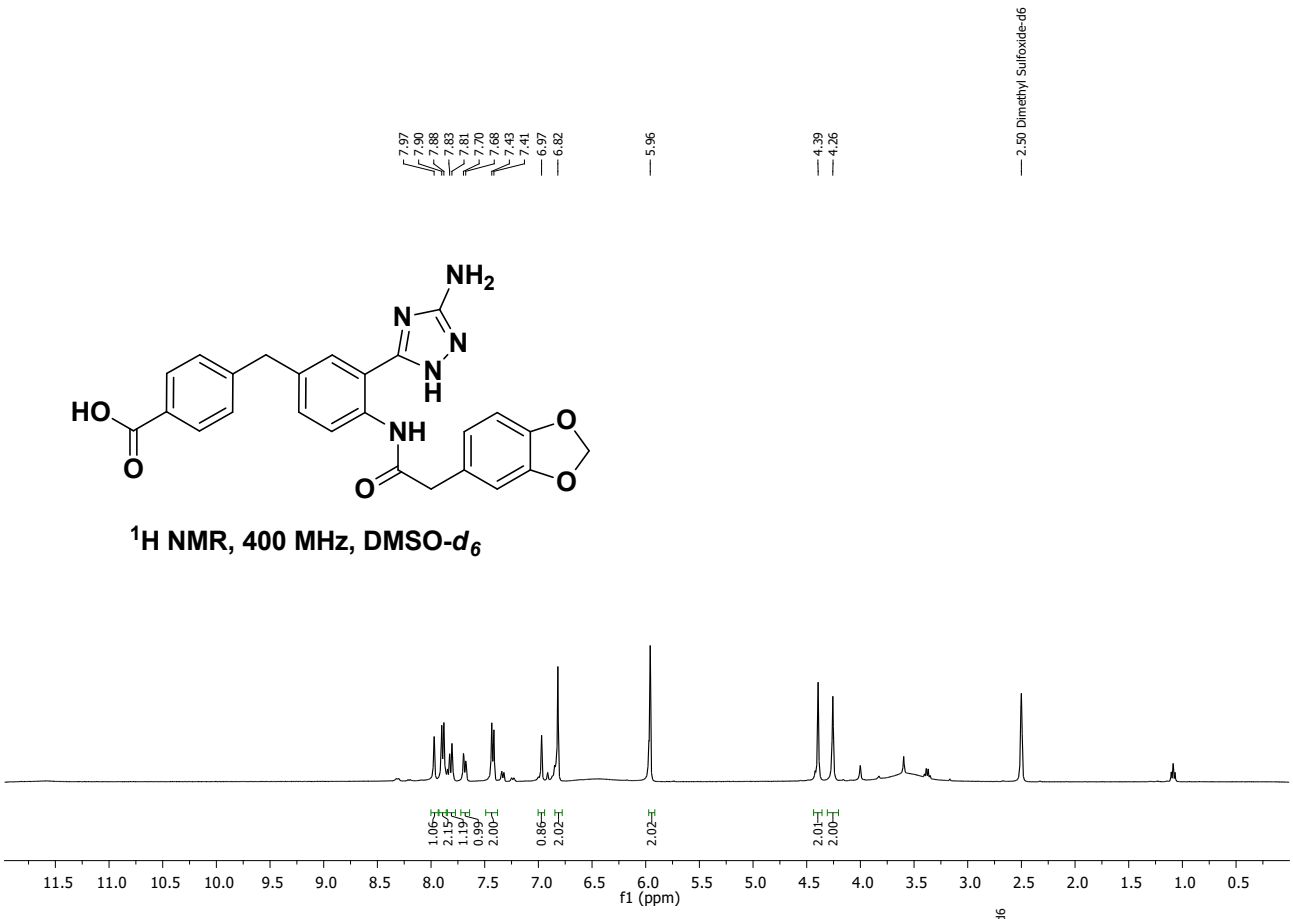




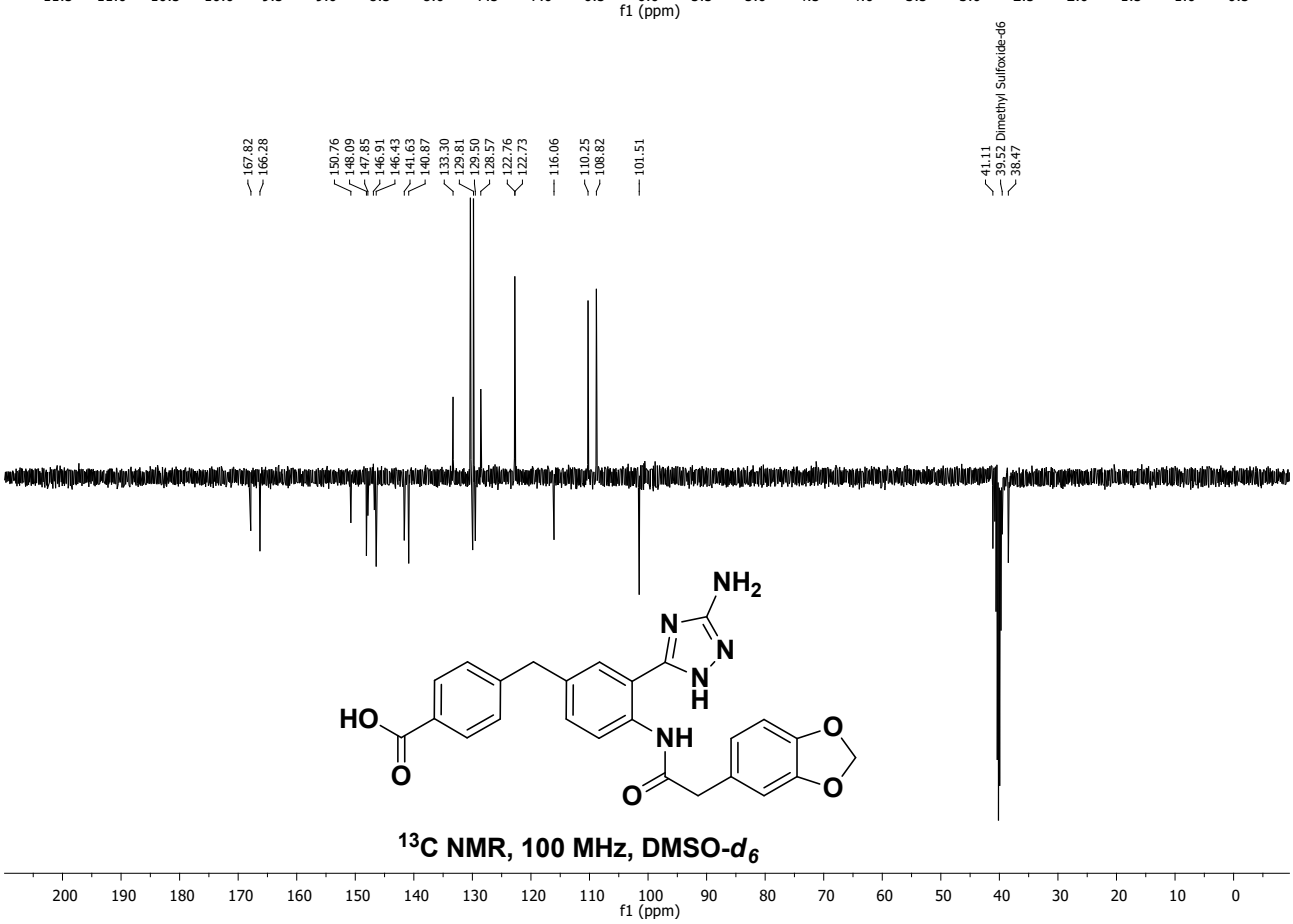


^{13}C NMR, 100 MHz, $CDCl_3$

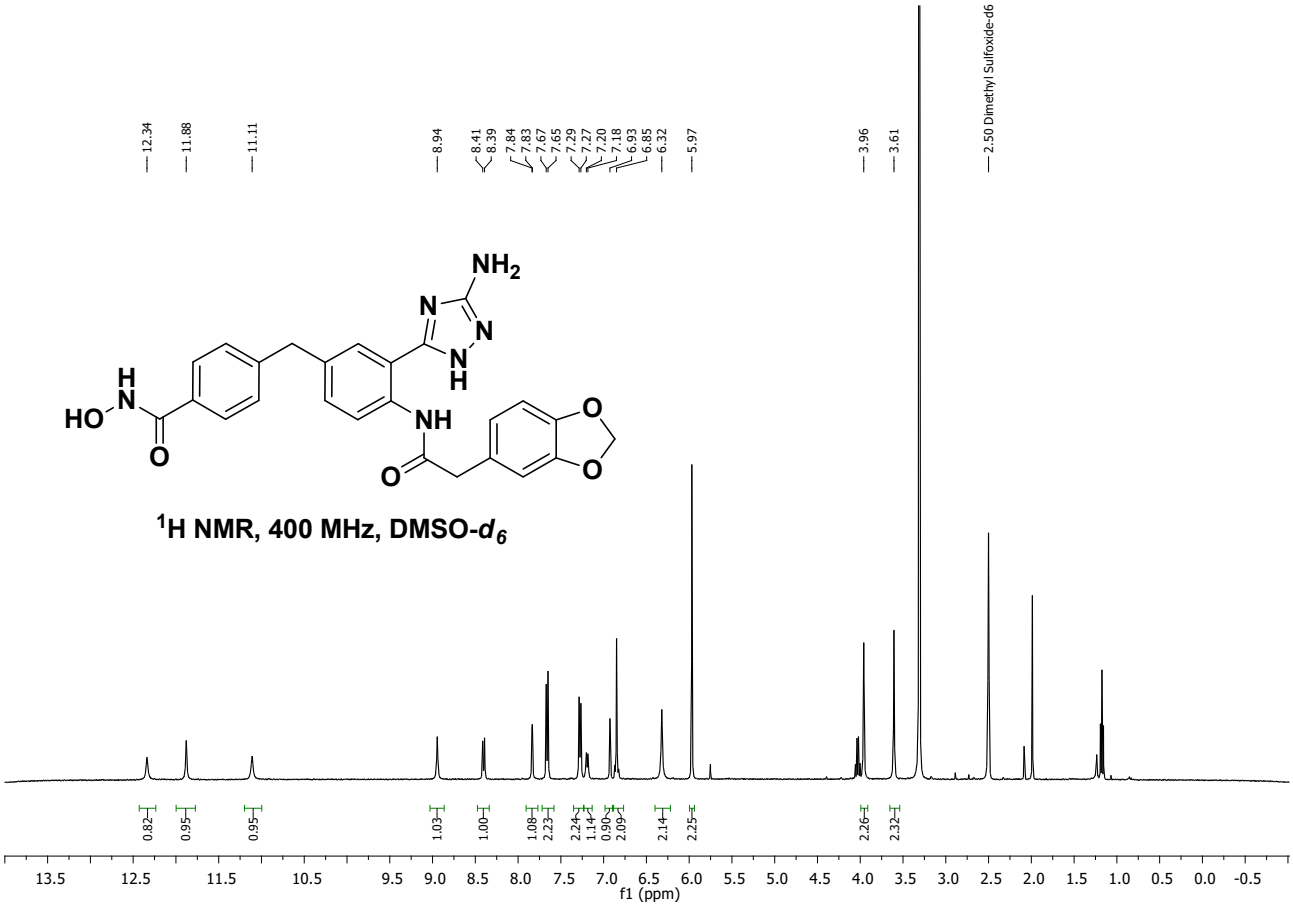




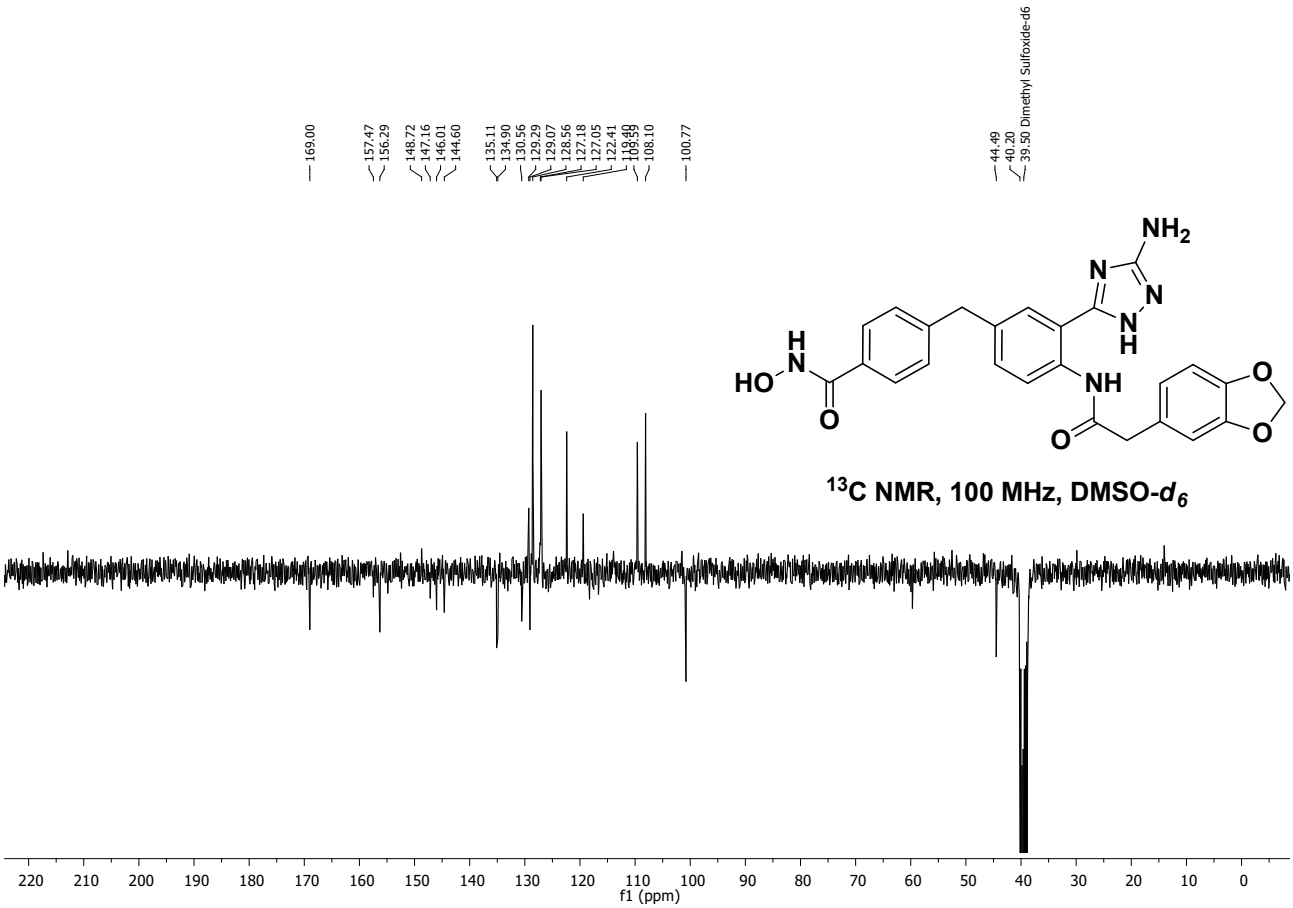
^{1}H NMR, 400 MHz, DMSO-*d*$_6$



^{13}C NMR, 100 MHz, DMSO-*d*$_6$



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



^{13}C NMR, 100 MHz, DMSO-*d*$_6$

HPLC-MS for 11a and 18