

In Vivo and Mechanistic Studies on Antitumor Lead

7-Methoxy-4-(2-methylquinazolin-4-yl)-3,4-dihydroquinoxalin-2(1H)-one and Its Modification as a Novel Class of Tubulin-binding Tumor-Vascular Disrupting Agents

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HPLC purity and conditions:

Purities of target compounds were determined by using an Agilent 1200 HPLC system with UV detector and an Agilent Eclipse XDB-C18 column (150 mm × 4.6 mm, 5 μm), flow rate 0.8 mL/min, UV detection at 254 nm, and injection volume of 15 μL.

Table S1 HPLC purity and HRMS data of target compounds

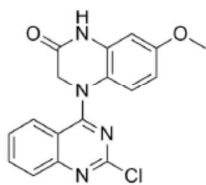
	Condition-1 (ACN/H ₂ O)			Condition-2 (MeOH/H ₂ O)			HRMS ^b m/z [M+1] ⁺	
	Solvent Ratio	Retention time (min)	Purity %	Solvent Ratio	Retention time (min)	Purity %	found	calculated
6a	60/40	3.090	98.2	70/30	5.030	100	341.0867 343.0843	341.0805
6b	60/40	2.435	97.5	70/30	4.121	98.5	336.1501	336.1460
6c	80/20	3.355	96.2	80/20	3.473	96.4	350.1626	350.1617
6d	70/30	11.509	97.8	80/20	5.186	96.4	378.2017	378.1930
6e	60/40	2.143	99.1	70/30	3.883	98.8	380.1730	380.1723
6f	60/40	4.224	95.0	80/20	3.356	96.4	362.1658	362.1617
6g	70/30	3.451	99.1	70/30	12.640	95.1	390.1984	390.1930
6h		ND ^a	ND	80/20	5.234	95.4	376.1784	376.1773
6i	60/40	5.626	95.6	80/20	4.439	95.2	412.1664	412.1585
6j	60/40	6.148	97.8	70/30	7.149	95.3	398.1441	398.1429
6k	60/40	2.749	96.0	70/30	5.466	95.2	392.1729	392.1723
6l	60/40	6.005	95.3	80/20	4.701	95.2	423.1649	423.1569
6m	50/50	3.977	96.6	70/30	14.433	95.8	423.1571	423.1569
6n	50/50	6.058	97.8	80/20	4.686	95.3	413.1799	413.1726
6o	50/50	3.226	96.2	70/30	7.090	93.2	351.1507	351.1457
6p	60/40	3.421	95.1	70/30	11.458	95.7	377.1615	377.1614
6q	50/50	3.132	95.7	70/30	3.741	95.5	379.1431	379.1406
6r	50/50	1.947	96.3	70/30	1.949	98.4	337.1290	337.1301
6s	50/50	4.758	95.7	70/30	3.042	95.1	451.2083	451.1981
6t	50/50	1.794	95.1	70/30	1.806	97.8	438.1866	438.1777

^a Not determined. ^b Measured on Waters Xevo G2 mass spectrometer.

Table S2. Data of compound **2** (XLWX132-18B) in NIH-NCI 60 cell line panel.

National Cancer Institute Developmental Therapeutics Program In-Vitro Testing Results															
NSC : D - 786094 / 1			Experiment ID : 1512RS19					Test Type : 08			Units : Molar				
Report Date : February 12, 2016			Test Date : December 14, 2015					QNS :			MC :				
COMI : XLWX132-18B			Stain Reagent : SRB Dual-Pass Related					SSPL : 0ZTF							
Log10 Concentration															
Panel/Cell Line	Time	Mean Optical Densities						Percent Growth					GI50	TGI	LC50
		Zero	Ctrl	-11.0	-10.0	-9.0	-8.0	-7.0	-11.0	-10.0	-9.0	-8.0			
Leukemia															
CCRFL-CEM	0.586	2.982	2.950	3.036	1.347	0.936	0.935	99	102	32	15	15	5.51E-10	> 1.00E-7	> 1.00E-7
HL-60(TB)	0.935	2.880	2.866	2.938	1.090	0.593	0.589	99	103	8	-37	-37	3.61E-10	1.51E-9	> 1.00E-7
K-562	0.223	1.920	1.888	1.901	0.408	0.383	0.361	98	99	11	9	8	3.59E-10	> 1.00E-7	> 1.00E-7
MOLT-4	0.567	2.240	2.359	2.223	1.175	0.701	0.691	107	99	36	8	7	6.05E-10	> 1.00E-7	> 1.00E-7
RPMI-8226	0.860	2.876	2.899	2.975	1.557	1.541	1.474	101	105	35	34	30	6.03E-10	> 1.00E-7	> 1.00E-7
SR	0.236	0.822	0.818	0.787	0.248	0.221	0.249	99	94	2	-6	2	3.01E-10	.	> 1.00E-7
Non-Small Cell Lung Cancer															
A549/ATCC	0.518	2.148	2.049	2.159	1.086	0.822	0.845	94	101	35	19	20	5.88E-10	> 1.00E-7	> 1.00E-7
EKVX	0.831	2.755	2.556	2.640	1.582	1.400	1.411	90	94	39	30	30	6.32E-10	> 1.00E-7	> 1.00E-7
HOP-62	1.231	2.666	2.449	2.571	1.829	1.596	1.651	85	93	42	25	29	6.90E-10	> 1.00E-7	> 1.00E-7
HOP-92	1.256	1.967	1.924	1.937	1.836	1.840	1.781	94	96	82	82	74	> 1.00E-7	> 1.00E-7	> 1.00E-7
NCI-H226	1.207	2.586	2.574	2.588	2.222	1.547	1.551	99	100	74	25	25	3.03E-9	> 1.00E-7	> 1.00E-7
NCI-H23	0.857	2.587	2.423	2.395	1.376	1.027	1.106	91	89	30	10	14	4.58E-10	> 1.00E-7	> 1.00E-7
NCI-H322M	0.912	2.211	2.195	2.214	1.532	1.383	1.403	99	100	48	36	38	9.04E-10	> 1.00E-7	> 1.00E-7
NCI-H460	0.279	2.690	2.842	2.886	0.547	0.433	0.414	106	108	11	6	6	3.97E-10	> 1.00E-7	> 1.00E-7
NCI-H522	1.189	2.734	2.629	2.553	1.290	1.145	1.246	93	88	7	-4	4	2.94E-10	.	> 1.00E-7
Colon Cancer															
COLO 205	0.383	1.478	1.432	1.458	0.420	0.234	0.237	96	98	3	-39	-38	3.22E-10	1.20E-9	> 1.00E-7
HCC-2998	0.503	1.607	1.468	1.510	0.712	0.581	0.615	87	91	19	7	10	3.71E-10	> 1.00E-7	> 1.00E-7
HCT-116	0.199	1.647	1.638	1.640	0.377	0.302	0.313	99	100	12	7	8	3.69E-10	> 1.00E-7	> 1.00E-7
HCT-15	0.490	3.042	2.852	2.948	1.029	0.711	0.753	93	96	21	9	10	4.13E-10	> 1.00E-7	> 1.00E-7
HT29	0.271	1.894	1.844	1.823	0.309	0.278	0.296	97	95	3	.	2	3.07E-10	> 1.00E-7	> 1.00E-7
KM12	0.478	2.690	2.770	2.503	0.825	0.530	0.564	104	92	16	2	4	3.53E-10	> 1.00E-7	> 1.00E-7
SW-620	0.285	2.019	2.057	2.079	0.731	0.747	0.662	102	103	26	27	22	4.87E-10	> 1.00E-7	> 1.00E-7
CNS Cancer															
SF-268	0.655	2.233	2.190	2.155	1.362	0.964	1.039	97	95	45	21	24	7.88E-10	> 1.00E-7	> 1.00E-7
SF-295	0.919	3.061	2.840	2.904	1.088	0.773	0.873	90	93	8	-16	-5	3.18E-10	2.14E-9	> 1.00E-7
SF-539	1.067	2.783	2.710	2.672	1.096	0.971	0.902	96	94	2	-9	-15	2.98E-10	1.44E-9	> 1.00E-7
SNB-19	0.652	1.920	1.853	1.910	1.146	0.925	1.001	95	99	39	21	28	6.55E-10	> 1.00E-7	> 1.00E-7
SNB-75	0.873	1.696	1.488	1.562	1.064	1.082	1.119	75	84	23	25	30	3.60E-10	> 1.00E-7	> 1.00E-7
U251	0.552	2.301	2.261	2.289	0.942	0.812	0.838	98	99	22	15	16	4.37E-10	> 1.00E-7	> 1.00E-7
Melanoma															
LOX IMVI	0.346	2.589	2.502	2.421	1.098	0.704	0.704	96	92	34	16	16	5.26E-10	> 1.00E-7	> 1.00E-7
MALME-3M	0.713	1.404	1.330	1.381	1.101	1.105	1.109	89	97	56	57	57	> 1.00E-7	> 1.00E-7	> 1.00E-7
M14	0.450	1.850	1.752	1.721	0.636	0.605	0.639	93	91	13	11	14	3.36E-10	> 1.00E-7	> 1.00E-7
MDA-MB-435	0.479	2.337	2.246	2.211	0.274	0.309	0.305	95	93	-43	-36	-36	2.08E-10	4.84E-10	> 1.00E-7
SK-MEL-28	0.622	1.795	1.773	1.763	1.299	1.348	1.287	98	97	58	62	57	> 1.00E-7	> 1.00E-7	> 1.00E-7
SK-MEL-5	0.749	2.847	2.804	2.947	1.038	0.471	0.450	98	105	14	37	-40	4.00E-10	1.86E-9	> 1.00E-7
UACC-257	1.118	2.242	2.207	2.235	1.834	1.879	1.919	97	99	64	68	71	> 1.00E-7	> 1.00E-7	> 1.00E-7
UACC-62	0.736	2.299	2.132	2.205	1.123	1.093	1.232	89	94	25	23	32	4.32E-10	> 1.00E-7	> 1.00E-7
Ovarian Cancer															
IGROV1	0.583	2.004	2.055	2.093	1.223	0.939	0.937	104	106	45	25	25	8.30E-10	> 1.00E-7	> 1.00E-7
OVCAR-3	0.530	1.680	1.765	1.651	0.455	0.397	0.364	107	97	-14	-25	-31	2.66E-10	7.46E-10	> 1.00E-7
OVCAR-4	0.846	1.813	1.742	1.805	1.380	1.249	1.275	93	99	55	42	44	2.43E-9	> 1.00E-7	> 1.00E-7
OVCAR-5	0.798	1.788	1.738	1.732	1.504	1.410	1.335	95	94	71	62	54	> 1.00E-7	> 1.00E-7	> 1.00E-7
OVCAR-8	0.630	2.409	2.454	2.472	1.148	0.954	0.928	103	104	29	18	17	5.24E-10	> 1.00E-7	> 1.00E-7
NCI/ADR-RES	0.629	2.250	2.176	2.149	0.668	0.530	0.705	95	94	2	-16	5	3.01E-10	.	> 1.00E-7
SK-OV-3	0.762	1.850	1.732	1.799	0.993	0.975	0.996	89	95	21	20	21	4.09E-10	> 1.00E-7	> 1.00E-7
Renal Cancer															
786-0	0.748	2.373	2.190	2.370	1.734	1.413	1.392	89	100	61	41	40	3.46E-9	> 1.00E-7	> 1.00E-7
A498	1.462	2.406	2.403	2.414	1.579	1.436	1.425	100	101	12	-2	-3	3.76E-10	7.49E-9	> 1.00E-7
ACHN	0.676	2.328	2.309	2.295	1.475	1.235	1.178	99	98	48	34	30	9.28E-10	> 1.00E-7	> 1.00E-7
CAKI-1	0.689	3.144	2.921	3.008	1.442	1.151	1.149	91	94	31	19	19	4.97E-10	> 1.00E-7	> 1.00E-7
RXF 393	0.765	1.541	1.555	1.544	0.549	0.992	1.037	102	100	-28	29	35	2.46E-10	.	> 1.00E-7
SN12C	0.756	2.158	2.039	2.132	1.459	1.153	1.181	92	98	50	28	30	1.01E-9	> 1.00E-7	> 1.00E-7
TK-10	1.087	2.413	2.297	2.301	1.959	2.001	2.022	91	92	66	69	71	> 1.00E-7	> 1.00E-7	> 1.00E-7
UO-31	1.139	2.600	2.440	2.509	2.091	1.870	1.841	89	94	65	50	48	1.00E-8	> 1.00E-7	> 1.00E-7
Prostate Cancer															
PC-3	0.539	2.135	2.162	2.173	1.133	1.049	1.057	102	102	37	32	32	6.36E-10	> 1.00E-7	> 1.00E-7
DU-145	0.492	2.166	2.280	2.232	0.756	0.368	0.526	107	104	16	-25	2	4.09E-10	.	> 1.00E-7
Breast Cancer															
MCF7	0.573	3.057	2.649	2.793	1.049	0.934	0.907	84	89	19	15	13	3.63E-10	> 1.00E-7	> 1.00E-7
MDA-MB-231/ATCC	0.658	1.443	1.413	1.478	1.033	0.684	0.689	96	104	48	3	4	9.14E-10	> 1.00E-7	> 1.00E-7
HS 578T	1.264	2.401	2.495	2.453	1.656	1.686	1.634	108	105	34	37	33	6.01E-10	> 1.00E-7	> 1.00E-7
BT-549	1.070	2.183	2.066	2.176	1.816	1.228	1.305	89	99	67	14	21	2.10E-9	> 1.00E-7	> 1.00E-7
T-47D	0.765	1.604	1.492	1.510	0.973	1.243	1.283	87	89	25	57	62	> 1.00E-7	> 1.00E-7	> 1.00E-7
MDA-MB-468	1.034	2.041	2.173	2.102	1.189	0.906	0.909	113	106	15	-12	-12	4.15E-10	3.57E-9	> 1.00E-7

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6a

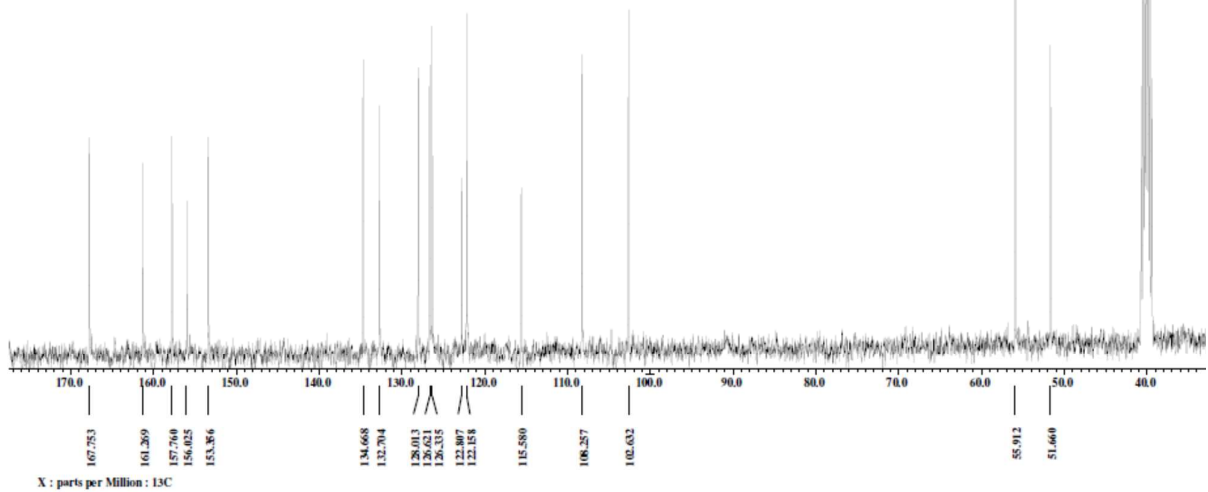


Figure S1. ^{13}C NMR spectra of **6a**

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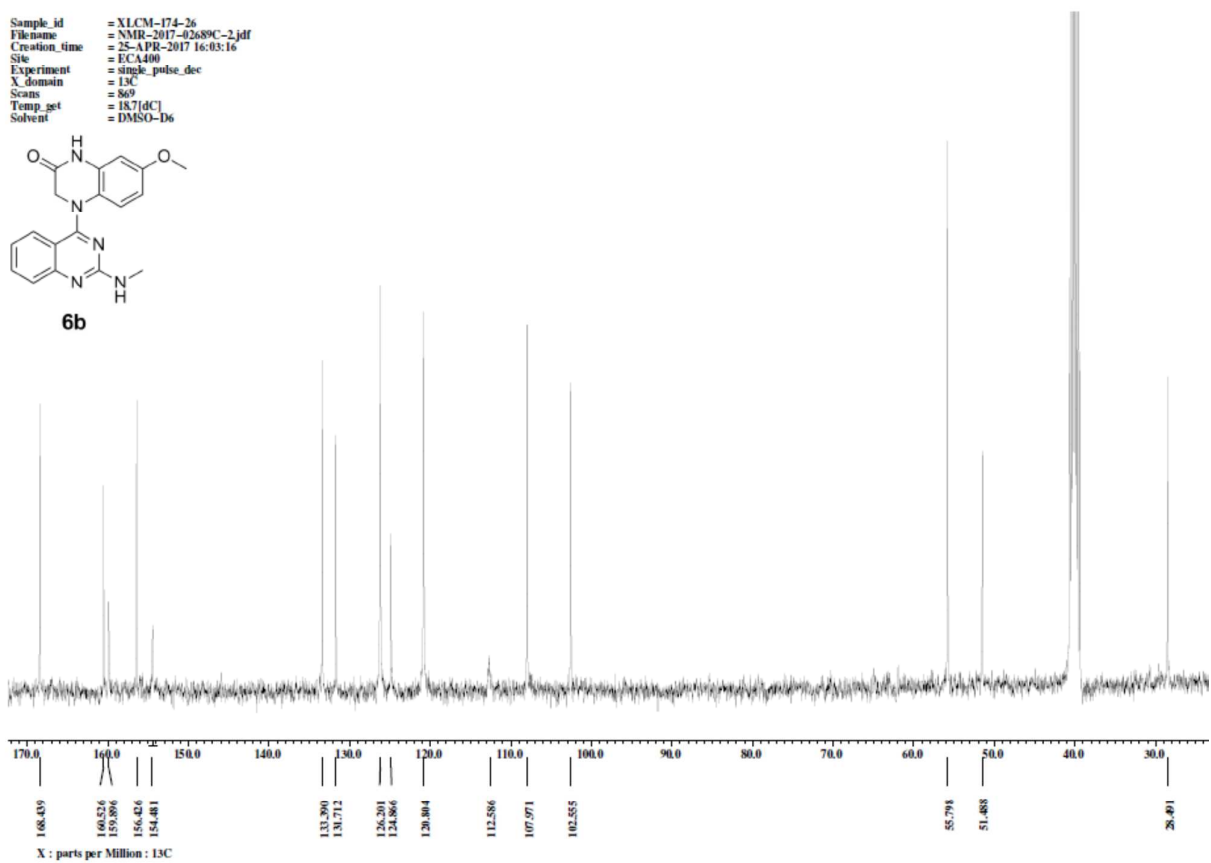
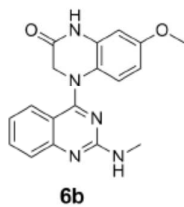


Figure S2. ^{13}C NMR spectra of **6b**

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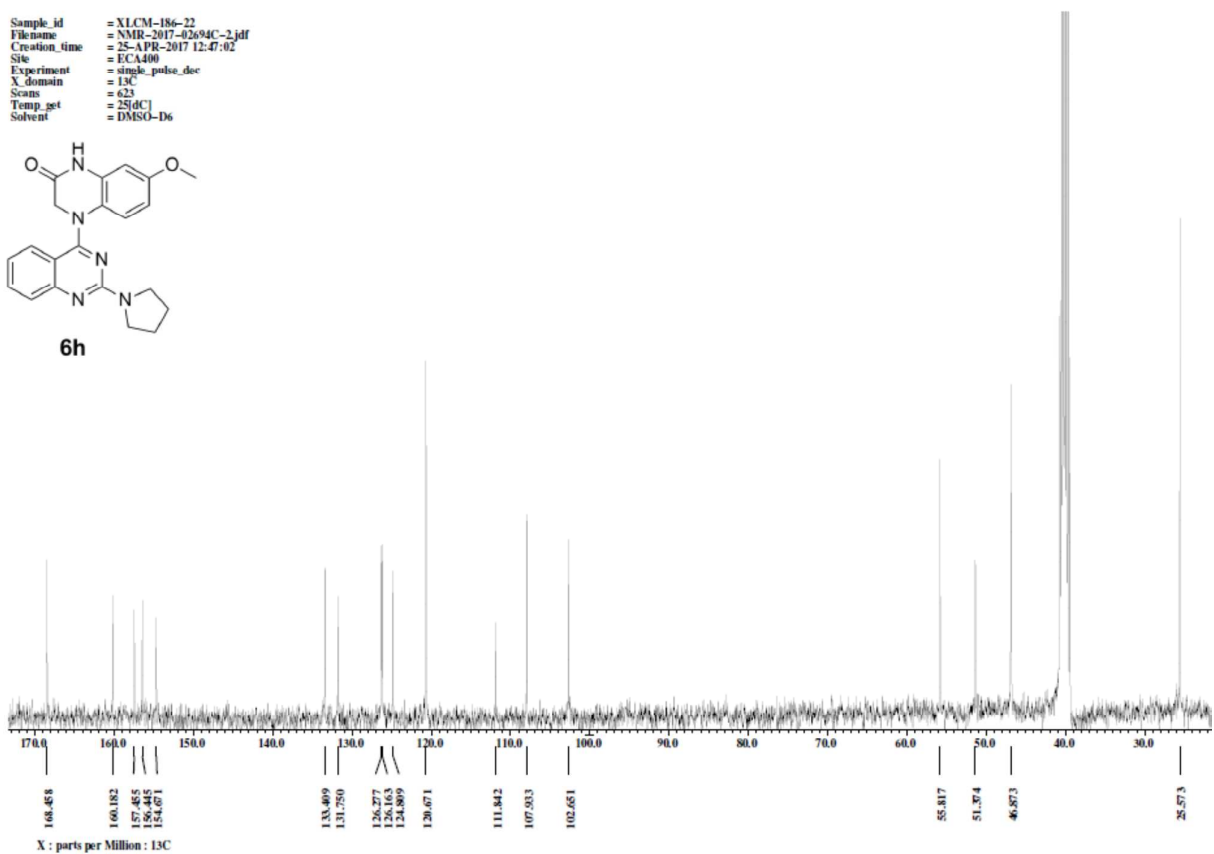
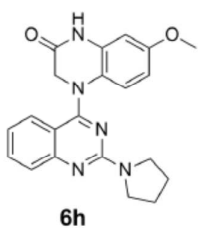


Figure S3. ^{13}C NMR spectra of **6h**

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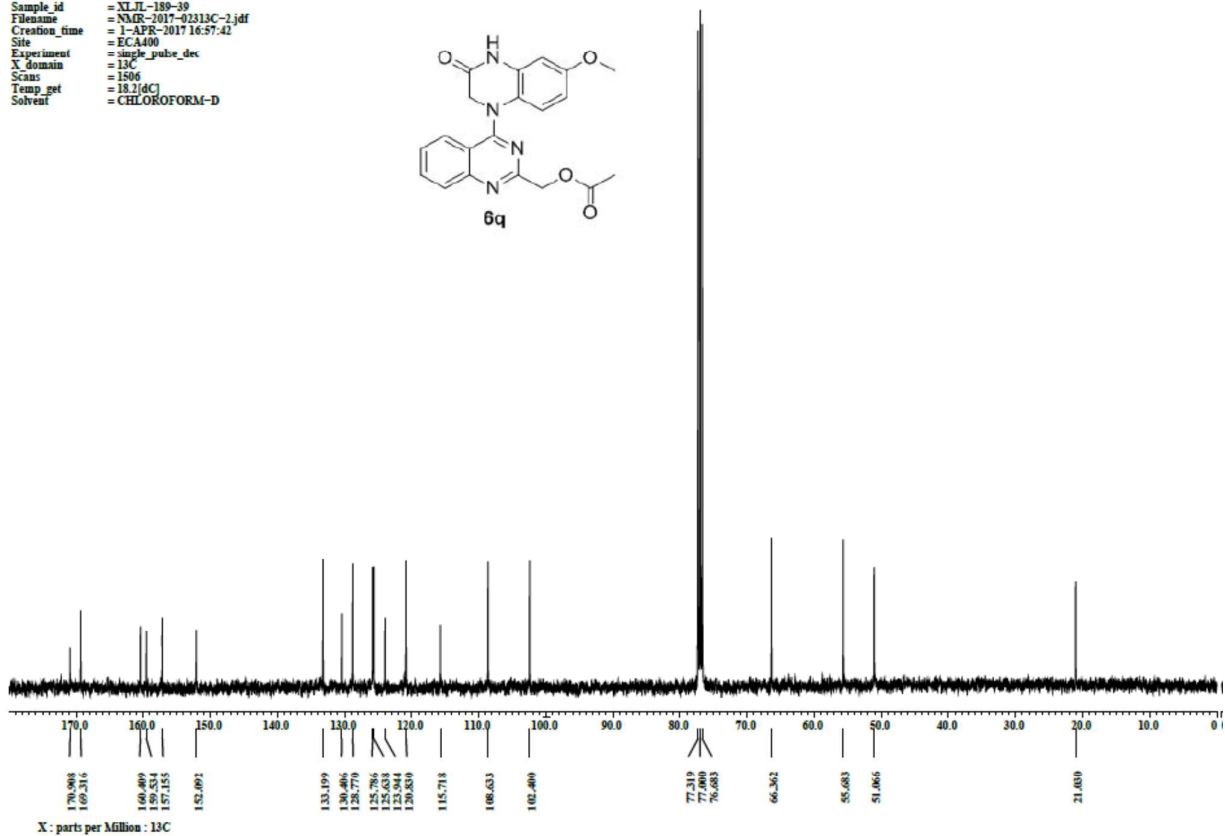
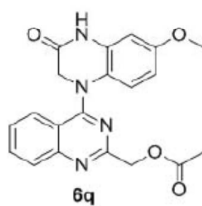


Figure S4. ^{13}C NMR spectra of **6q**

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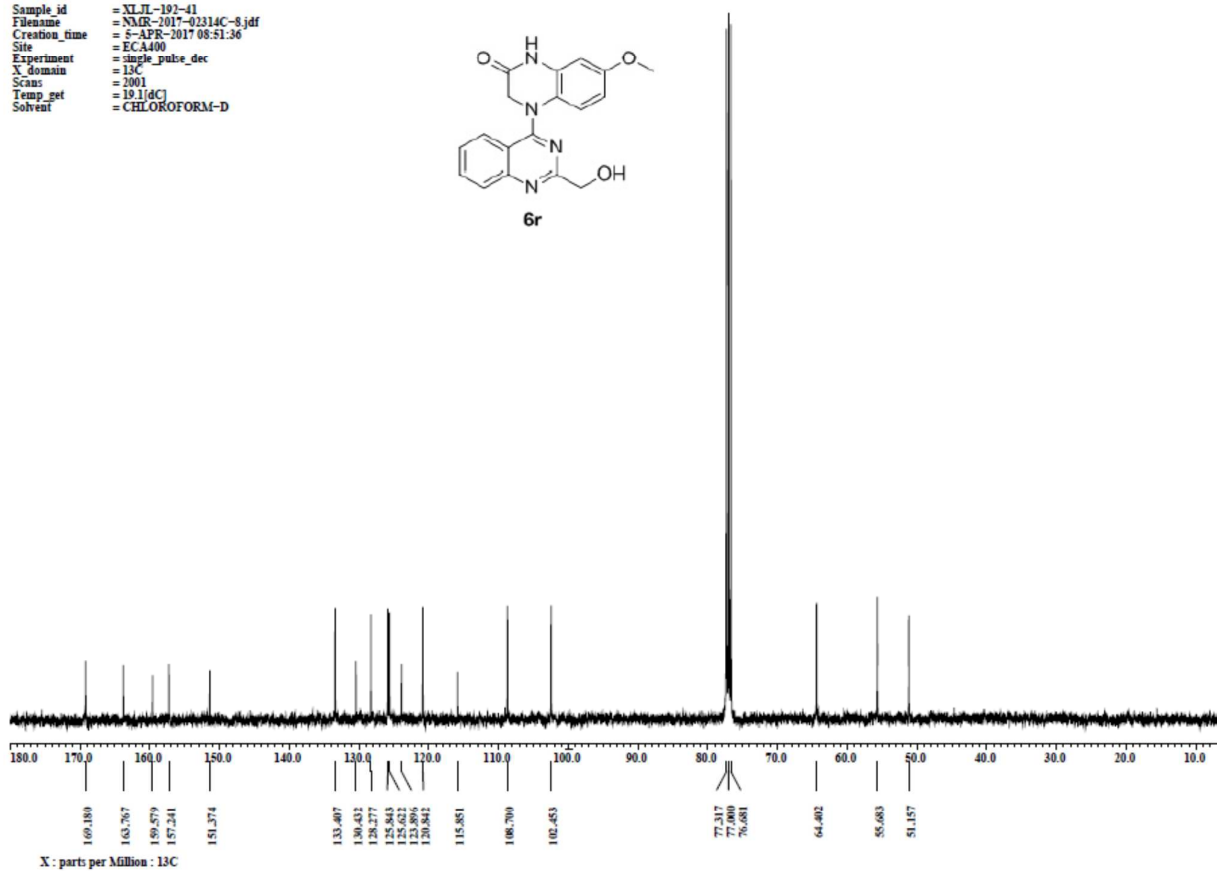
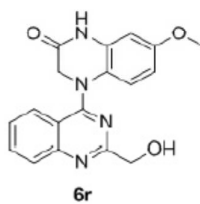


Figure S5. ^{13}C NMR spectra of **6r**

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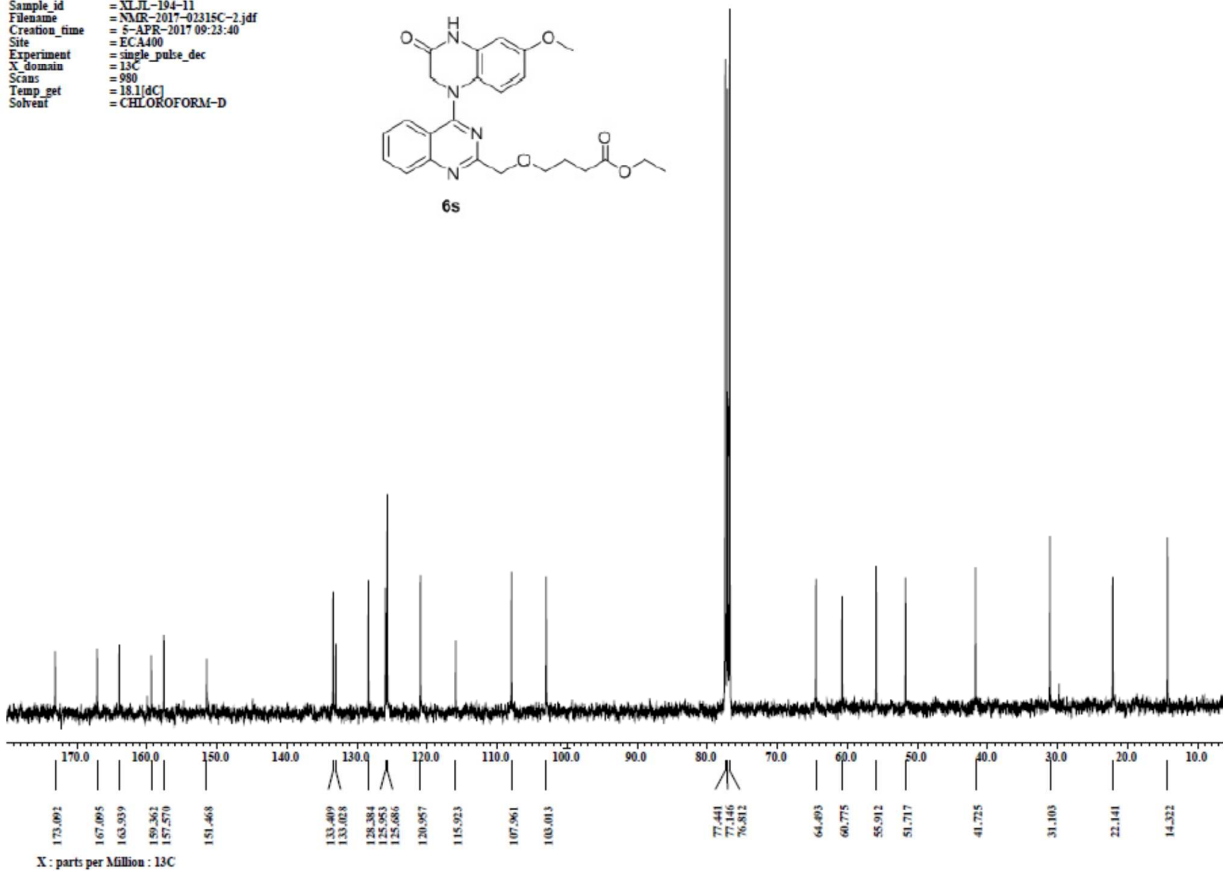
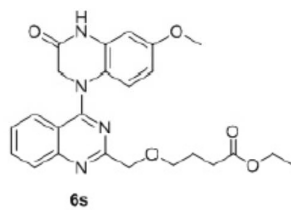


Figure S6. ^{13}C NMR spectra of **6s**