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Isoquinolinequinone *N*-oxides as Anticancer Agents Effective Against Drug Resistant Cell Lines

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and Florence O. McCarthy ^{*a}

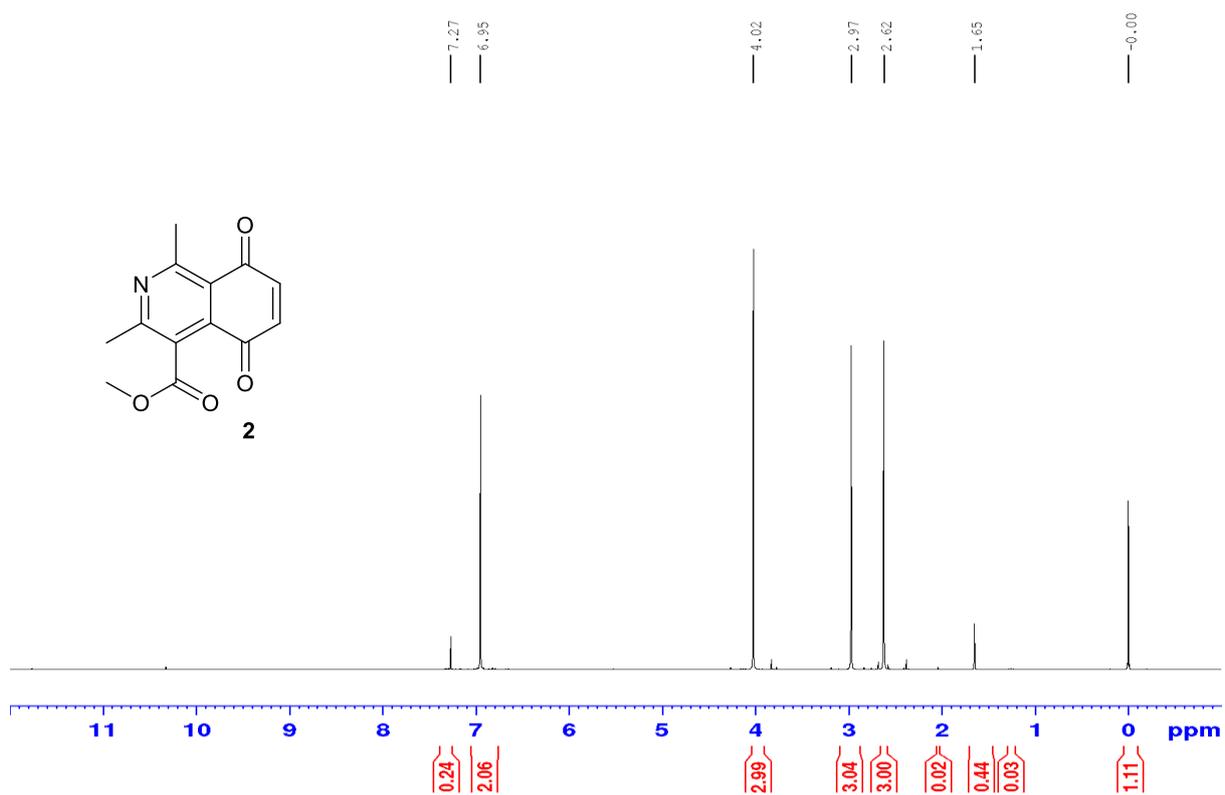
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*Correspondence: f.mccarthy@ucc.ie; Tel.: 00353214901695

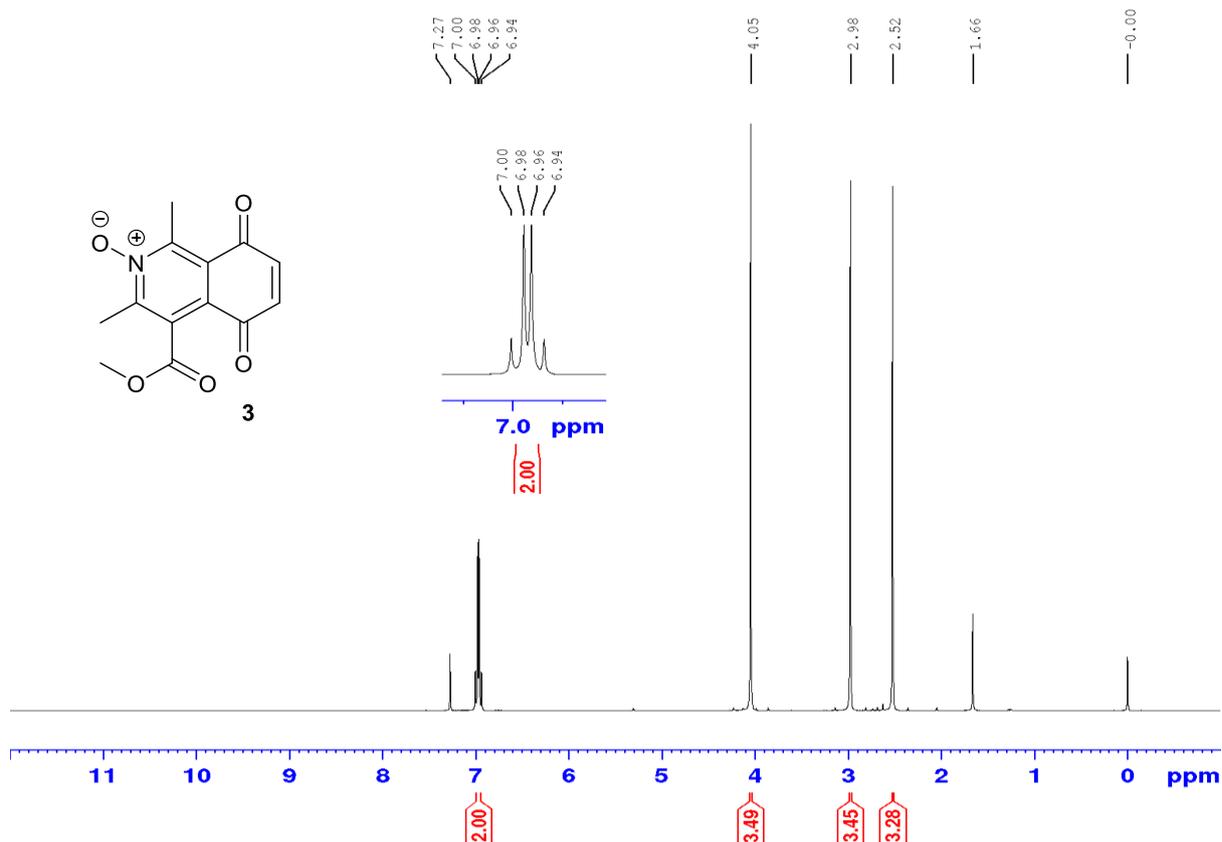
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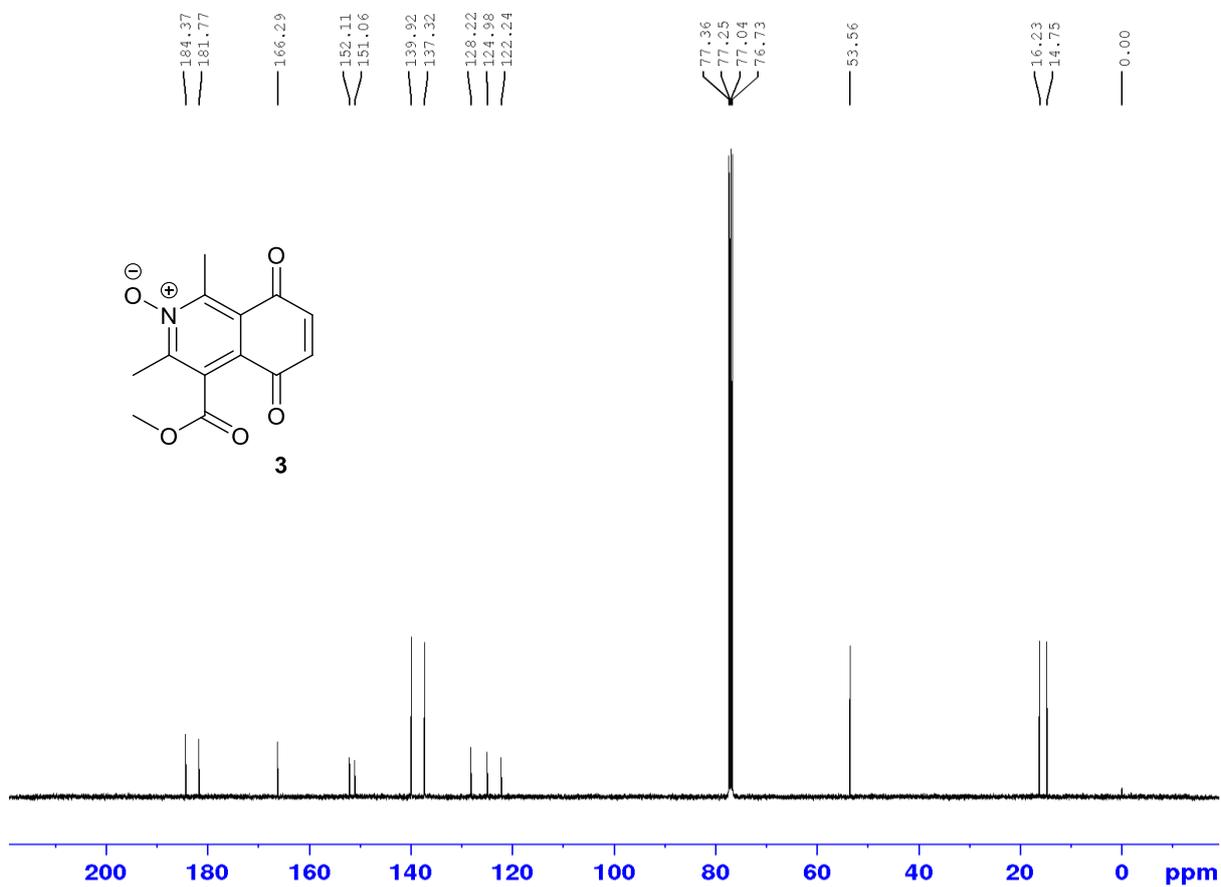
¹H NMR of 2



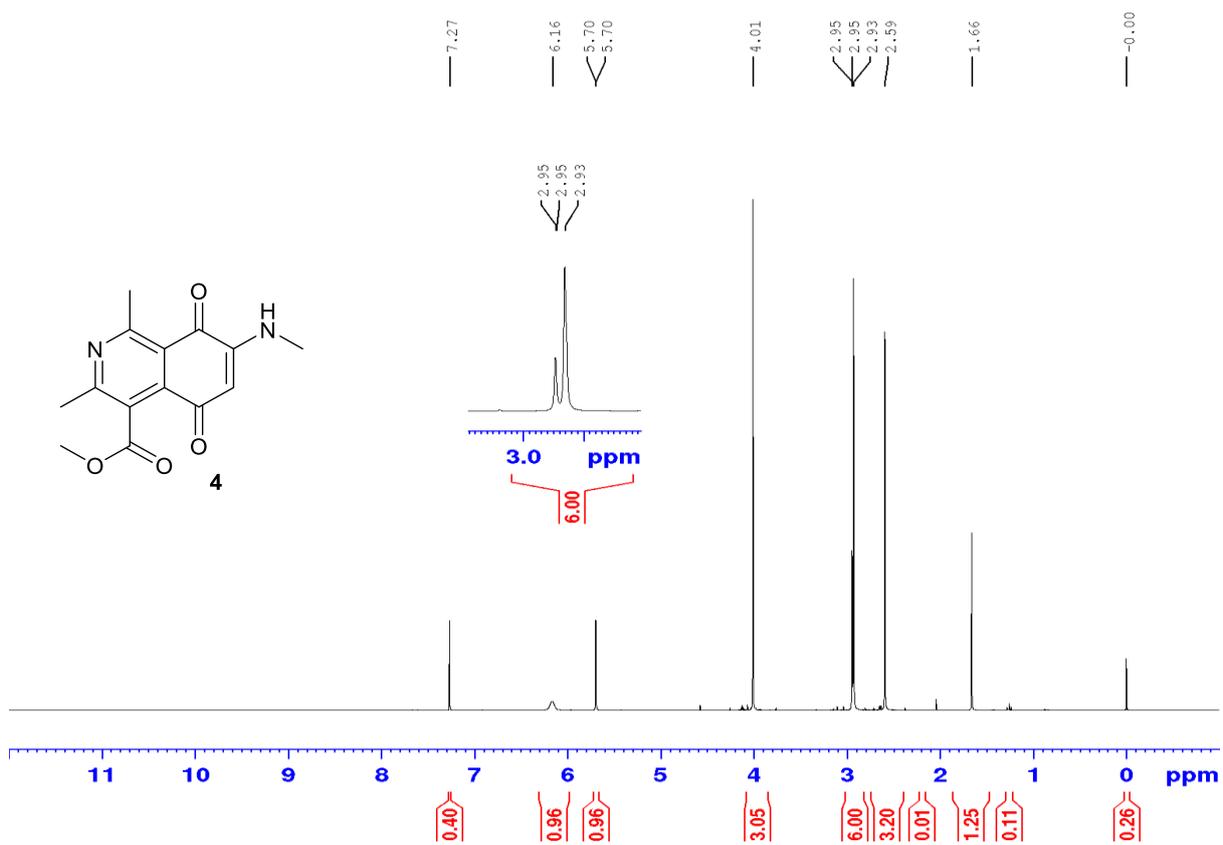
¹H NMR of **3**



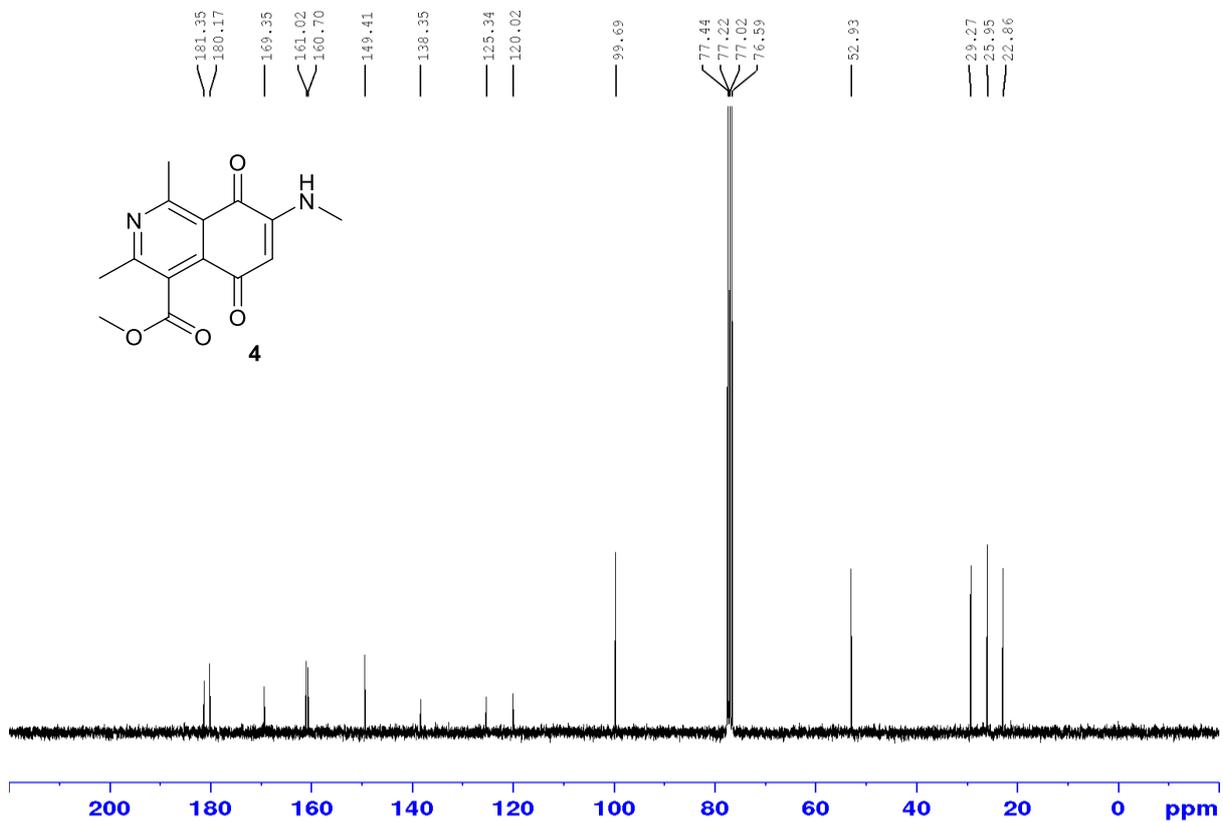
¹³C NMR of **3**



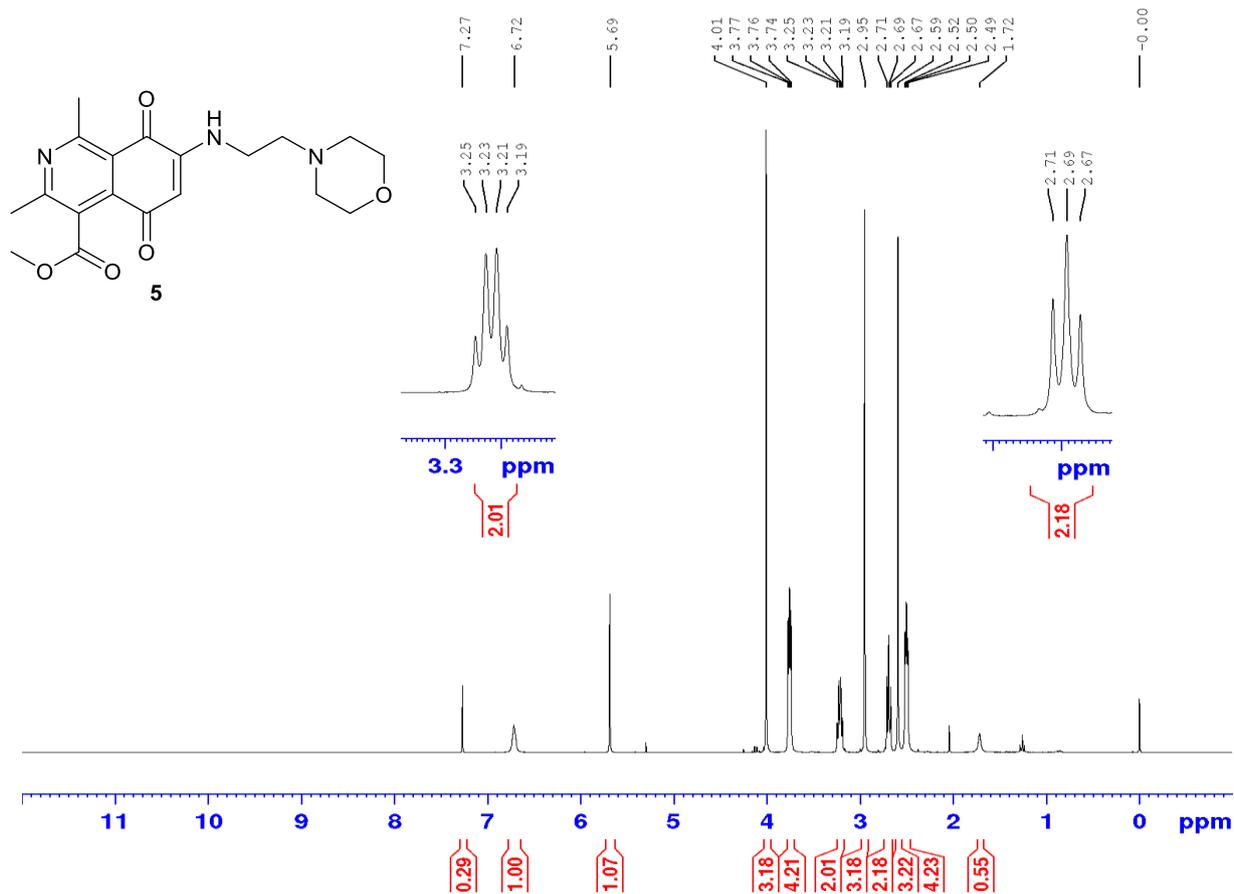
¹H NMR of 4



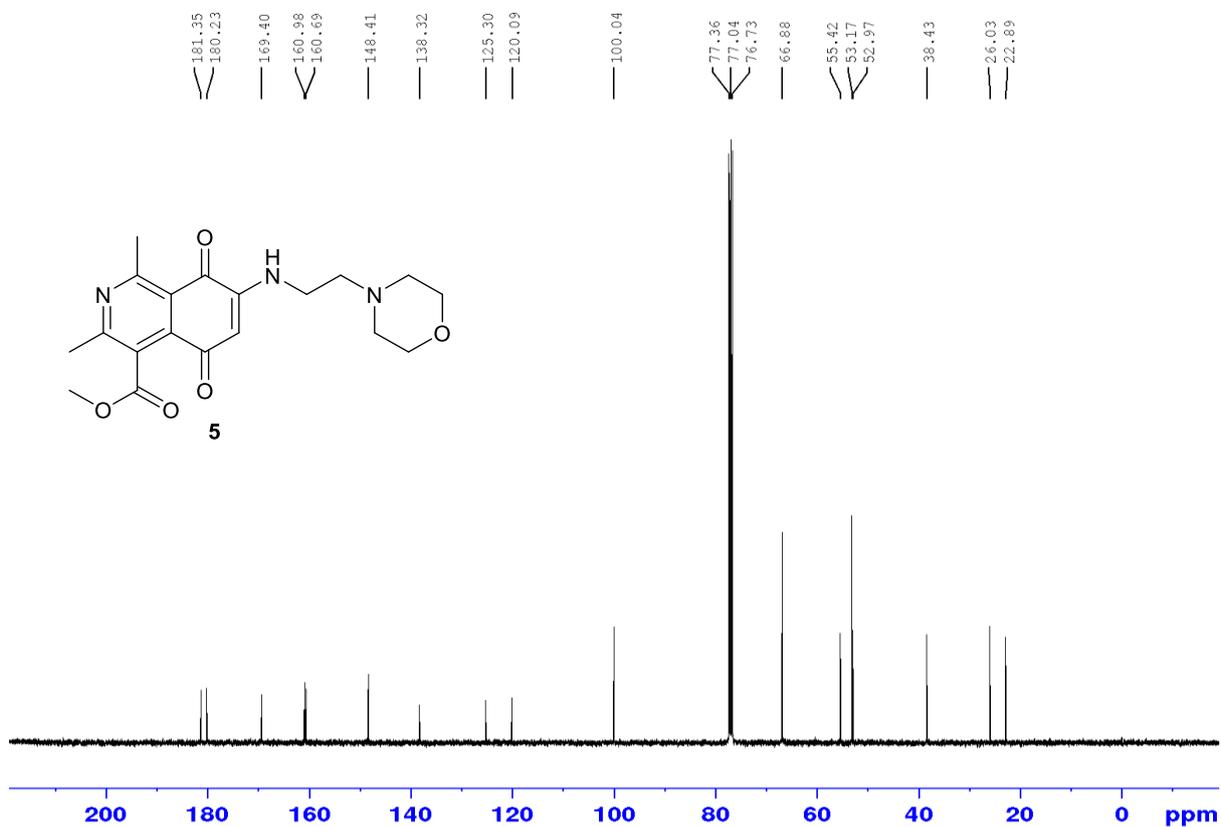
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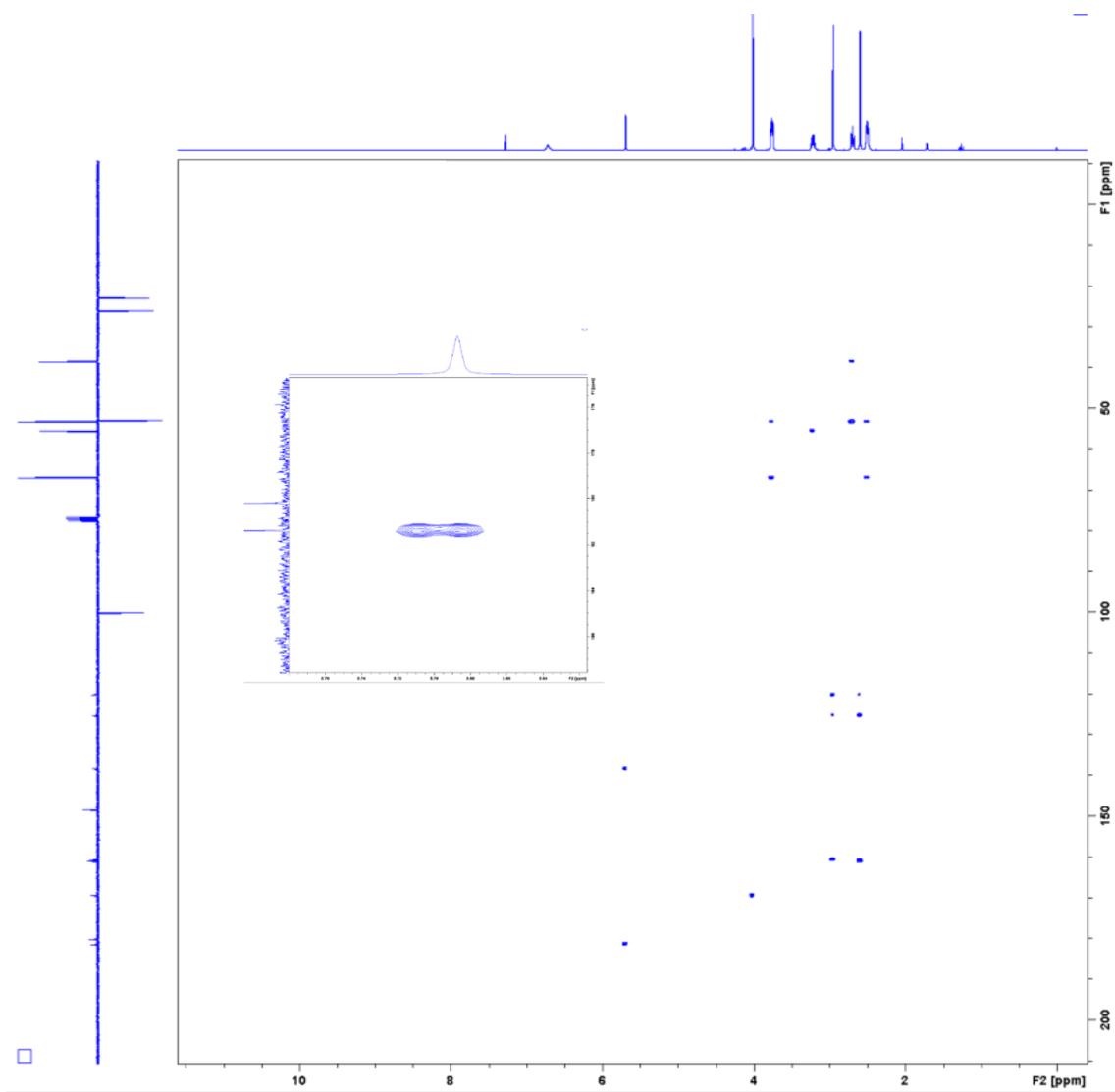
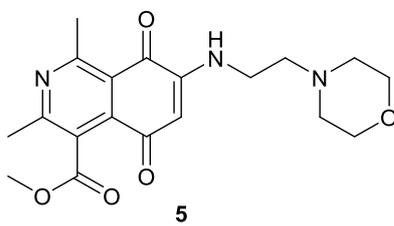
¹H NMR of 5



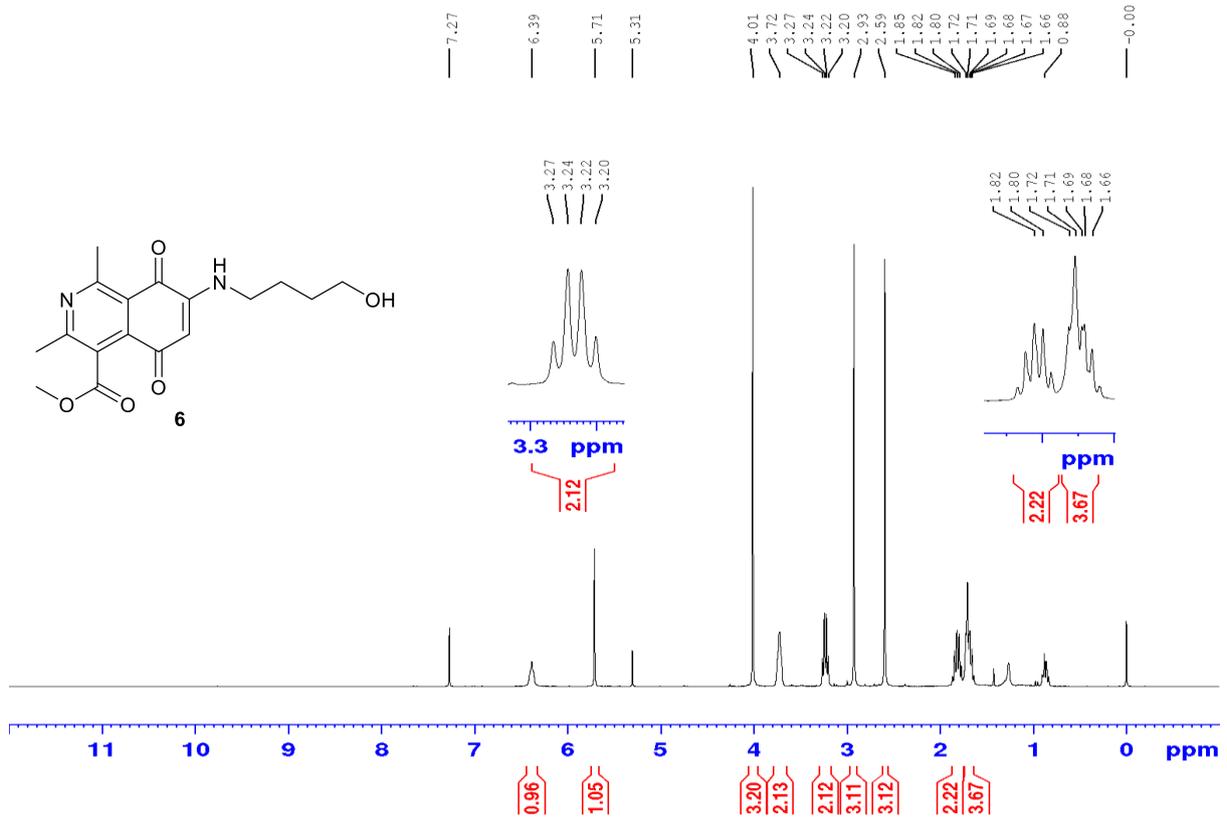
¹³C NMR of 5



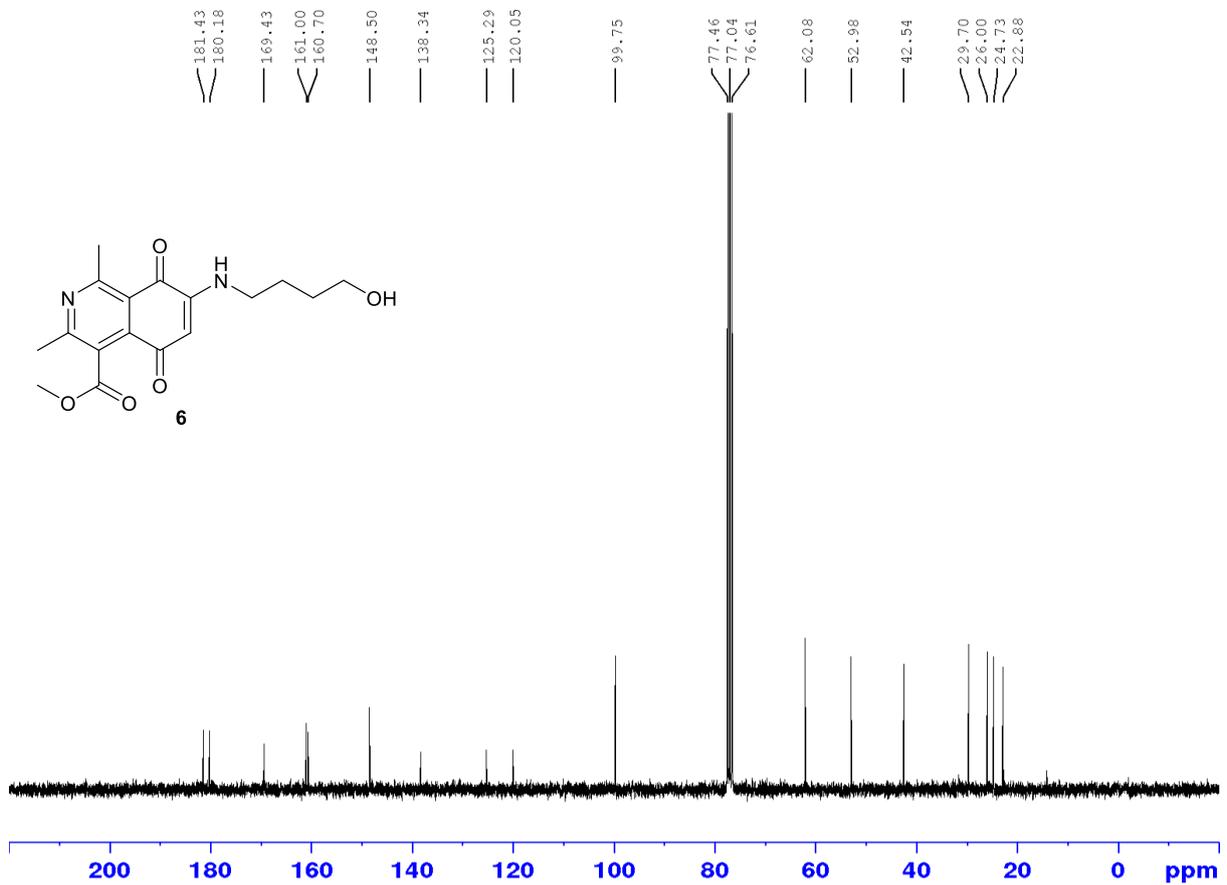
2D NMR- HMBC OF 5



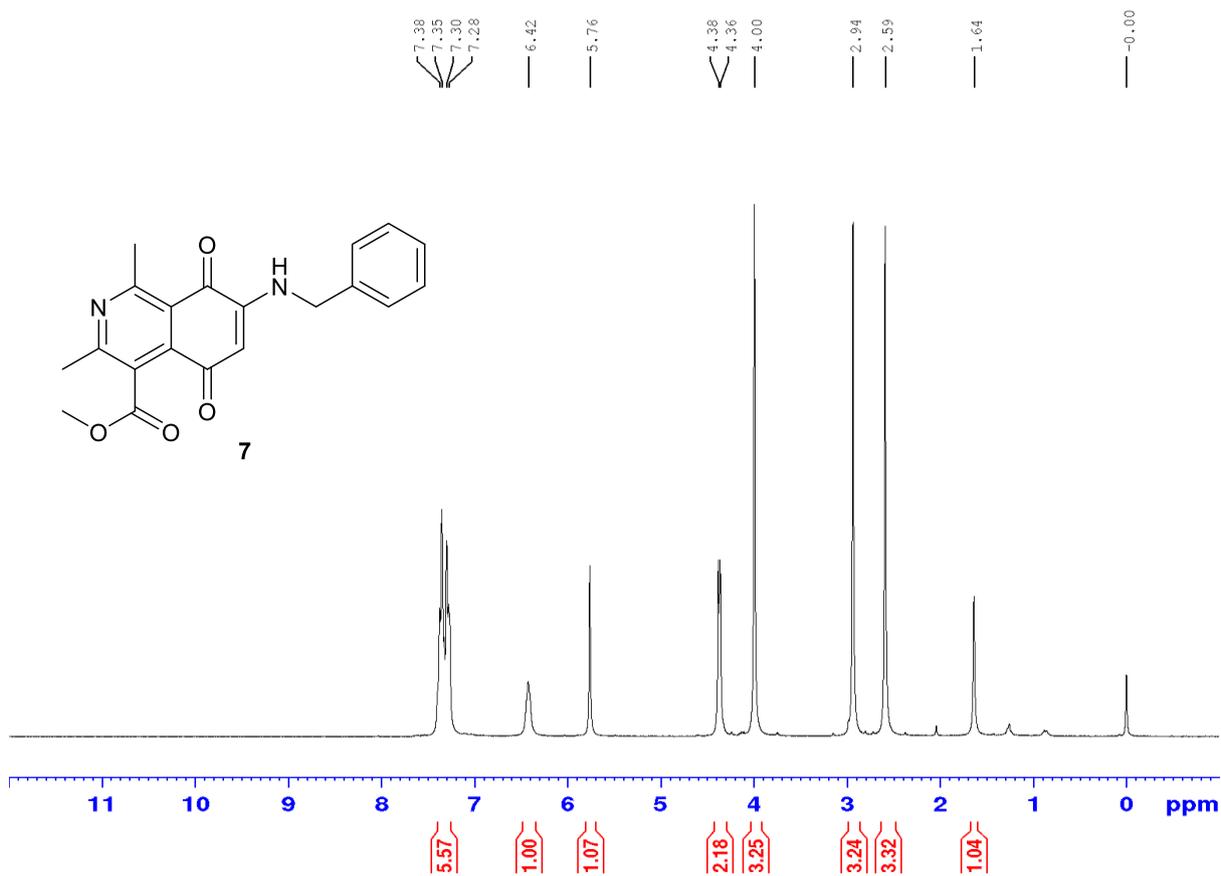
¹H NMR of 6



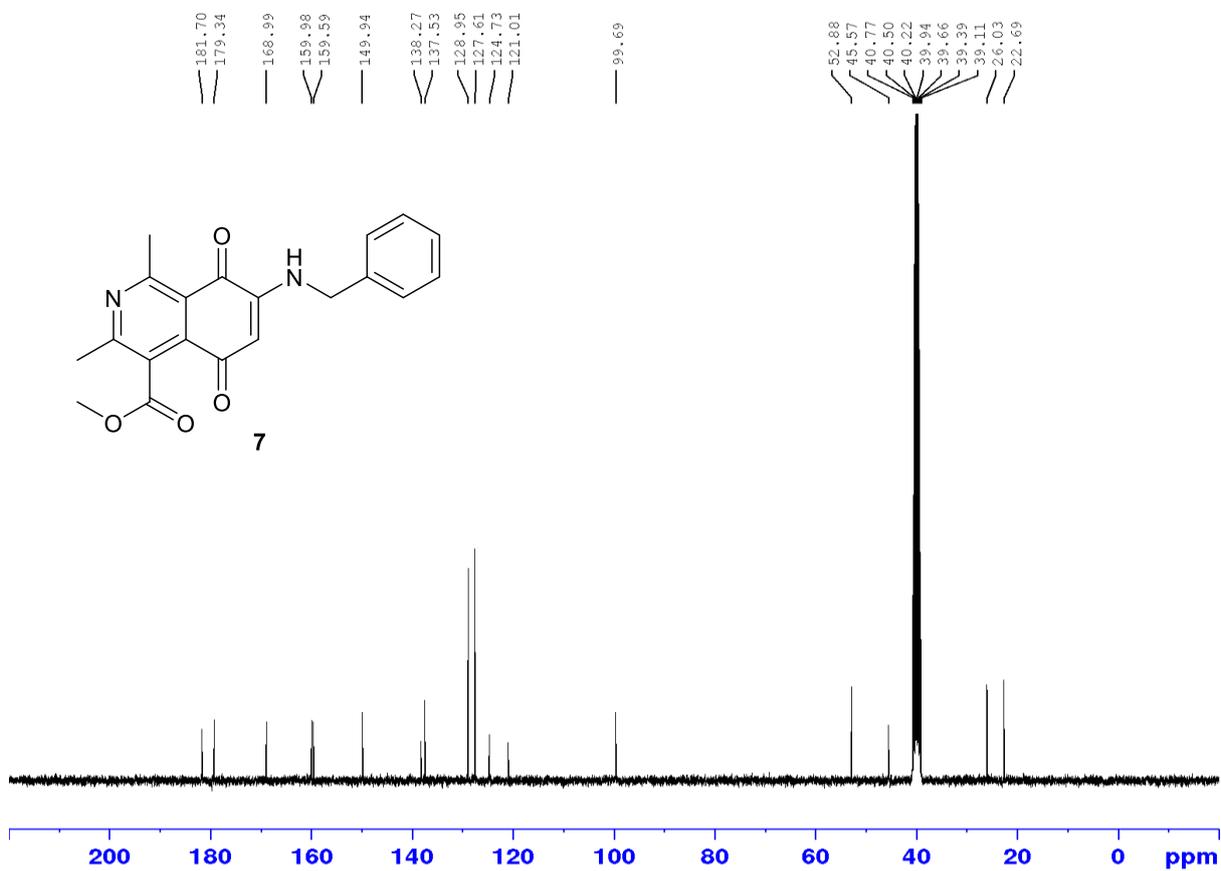
¹³C NMR of 6



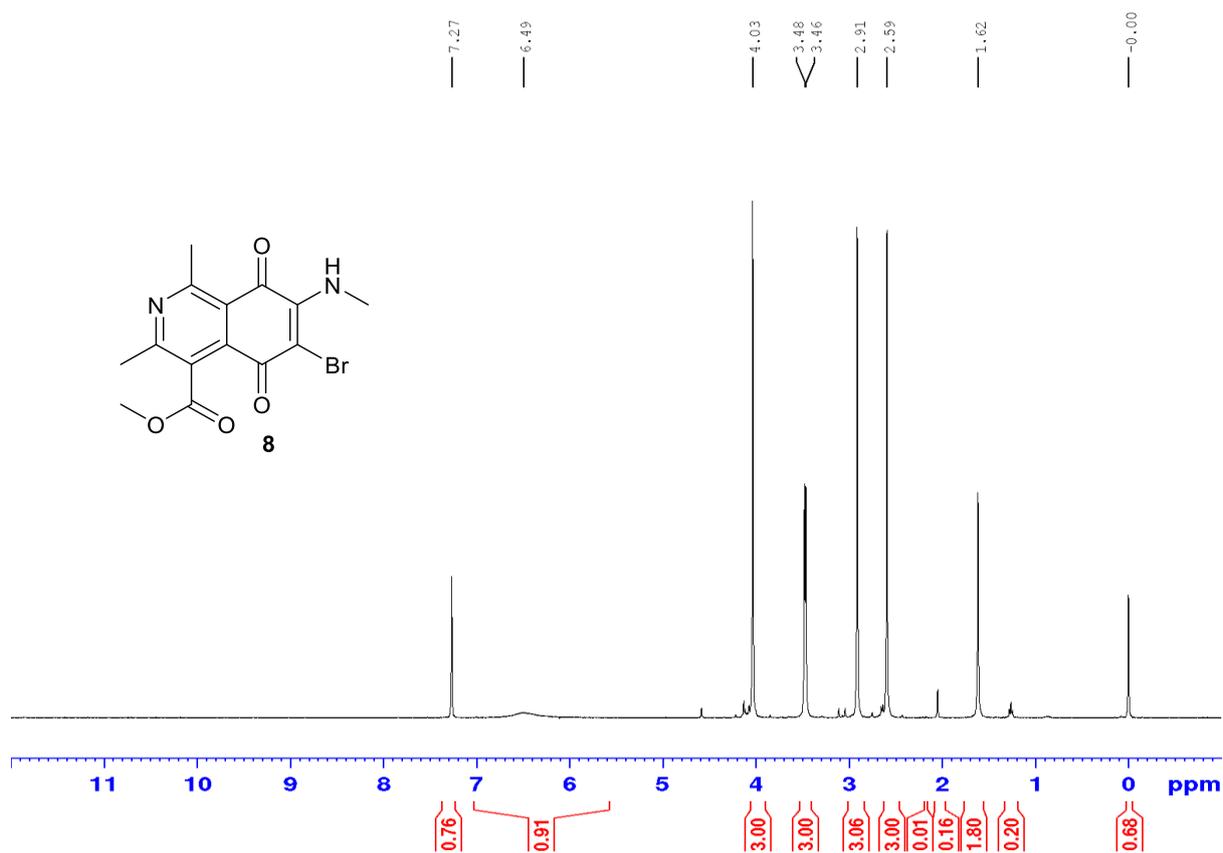
¹H NMR of 7



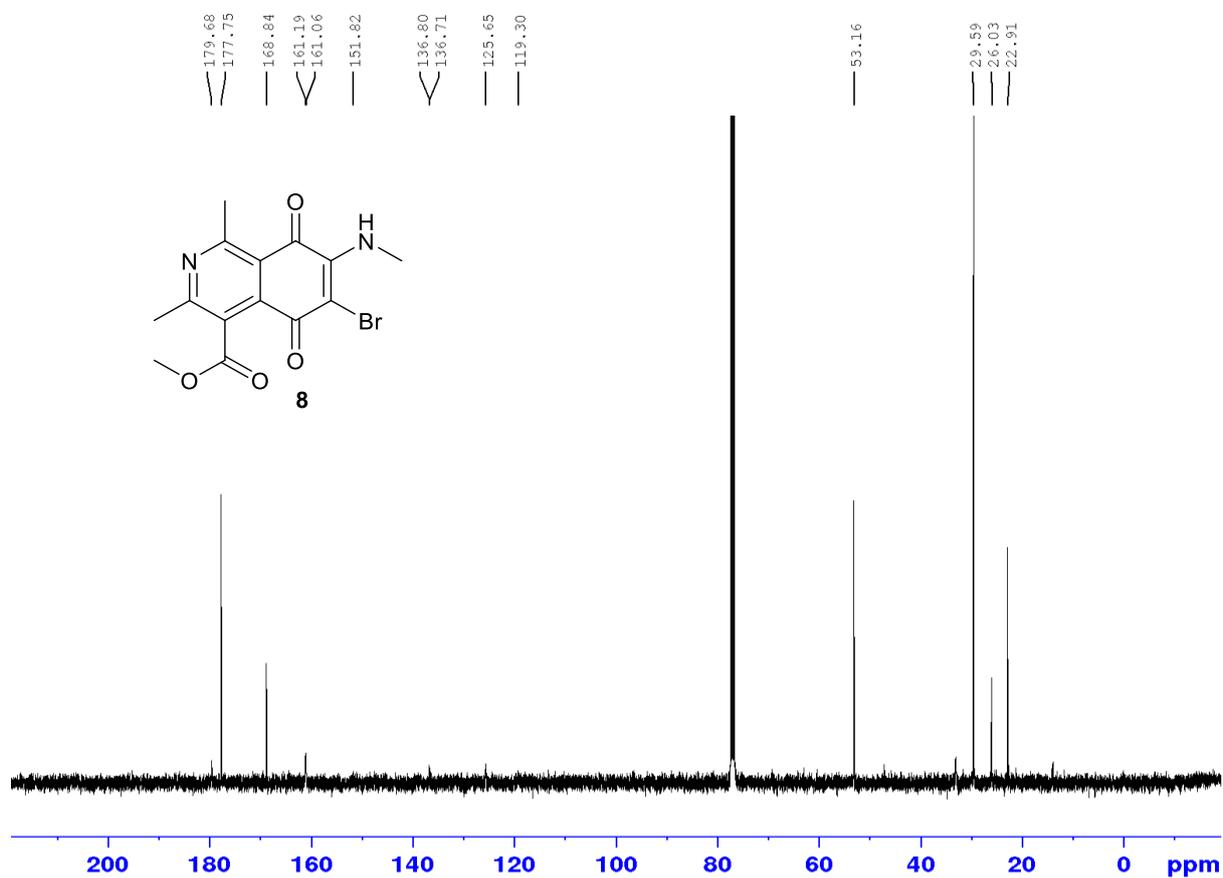
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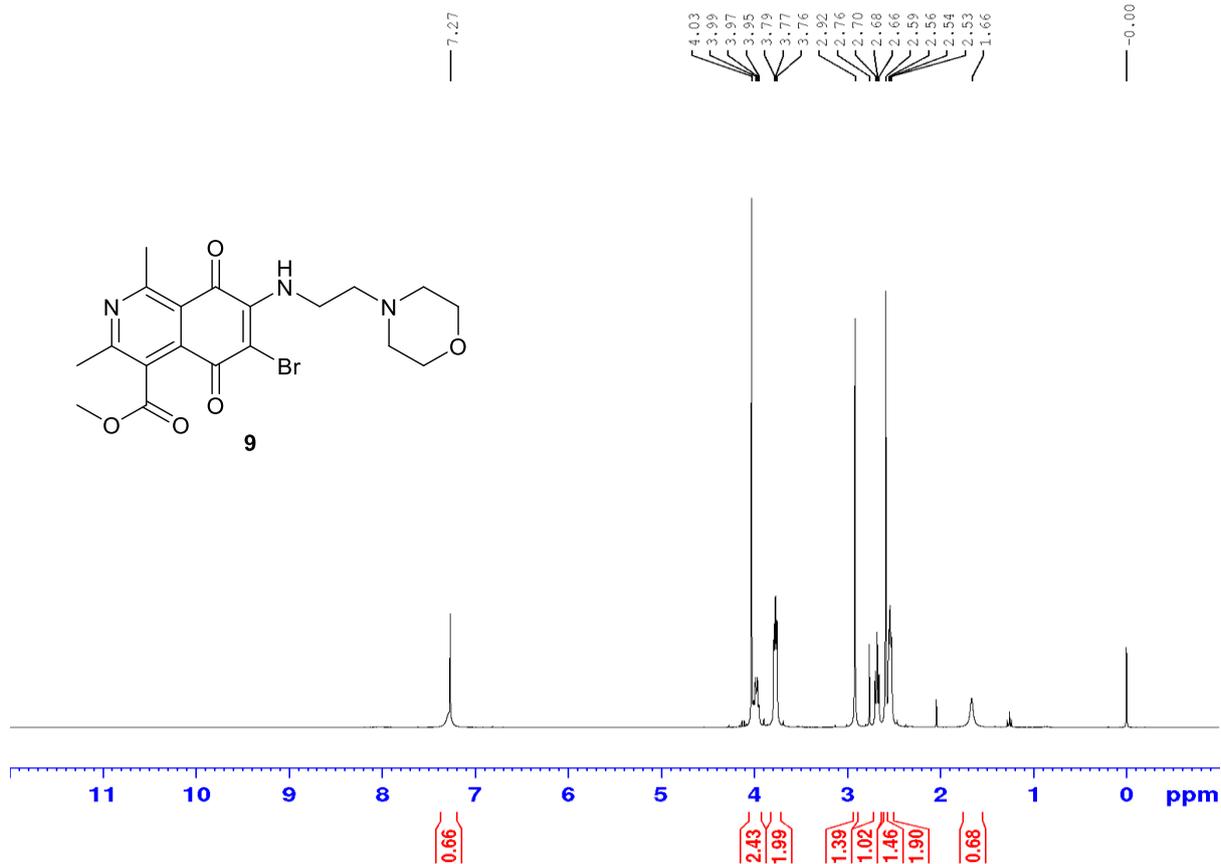
¹H NMR of **8**



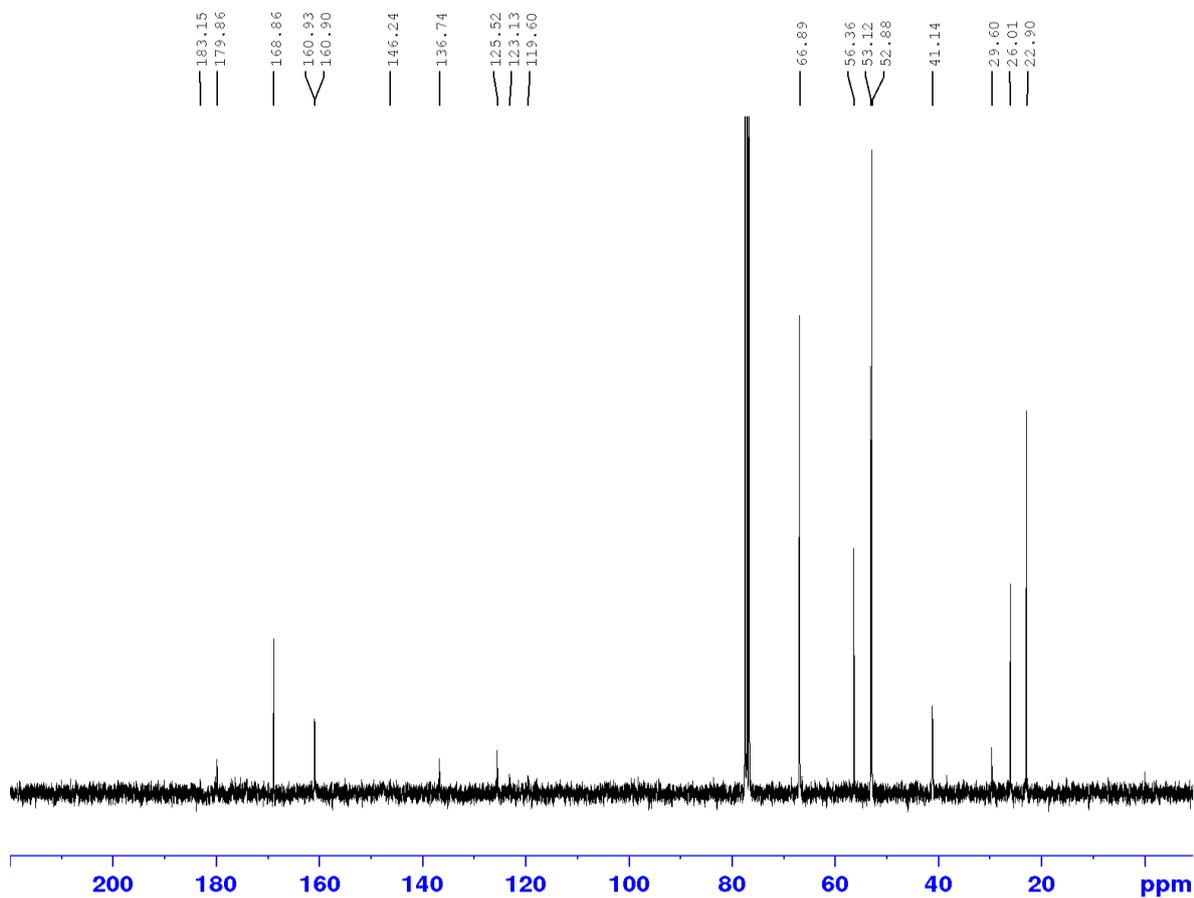
¹³C NMR of **8**



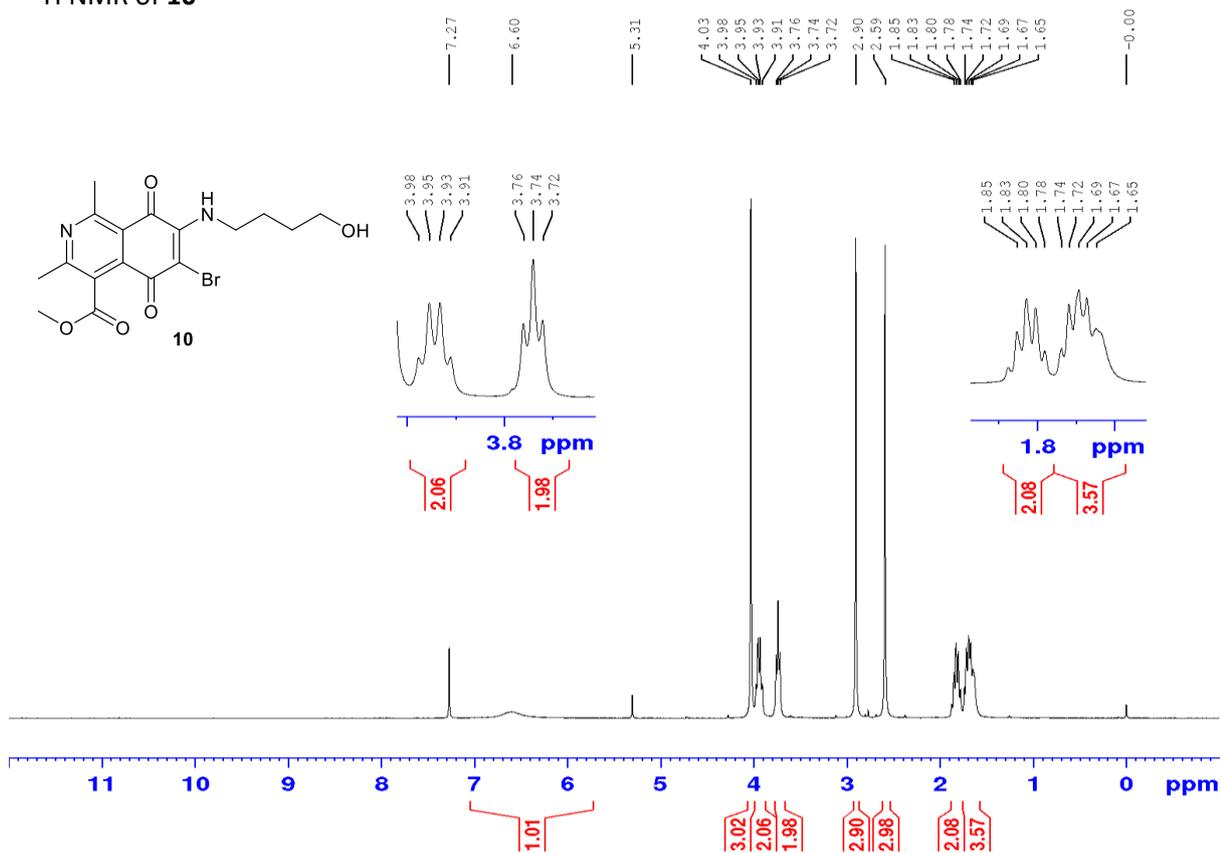
¹H NMR of 9



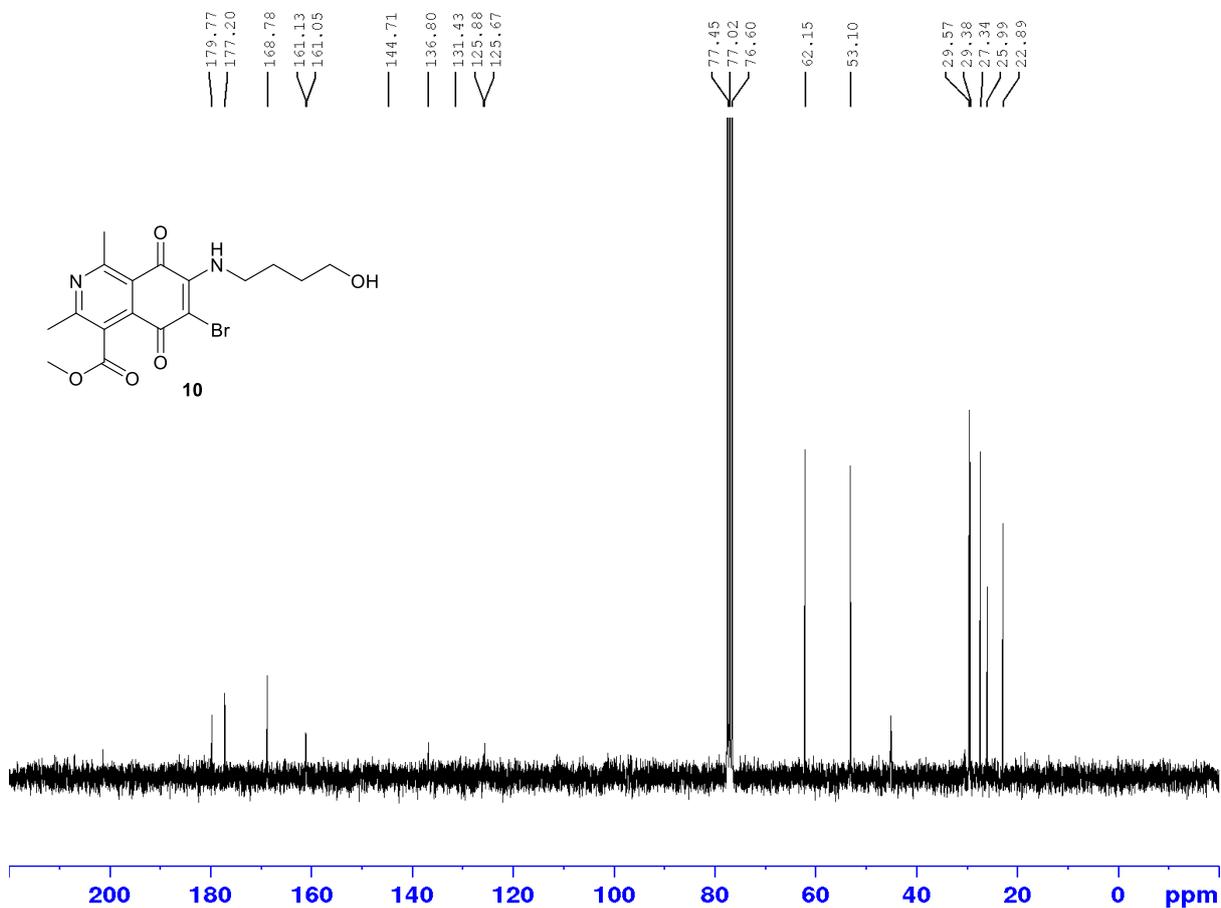
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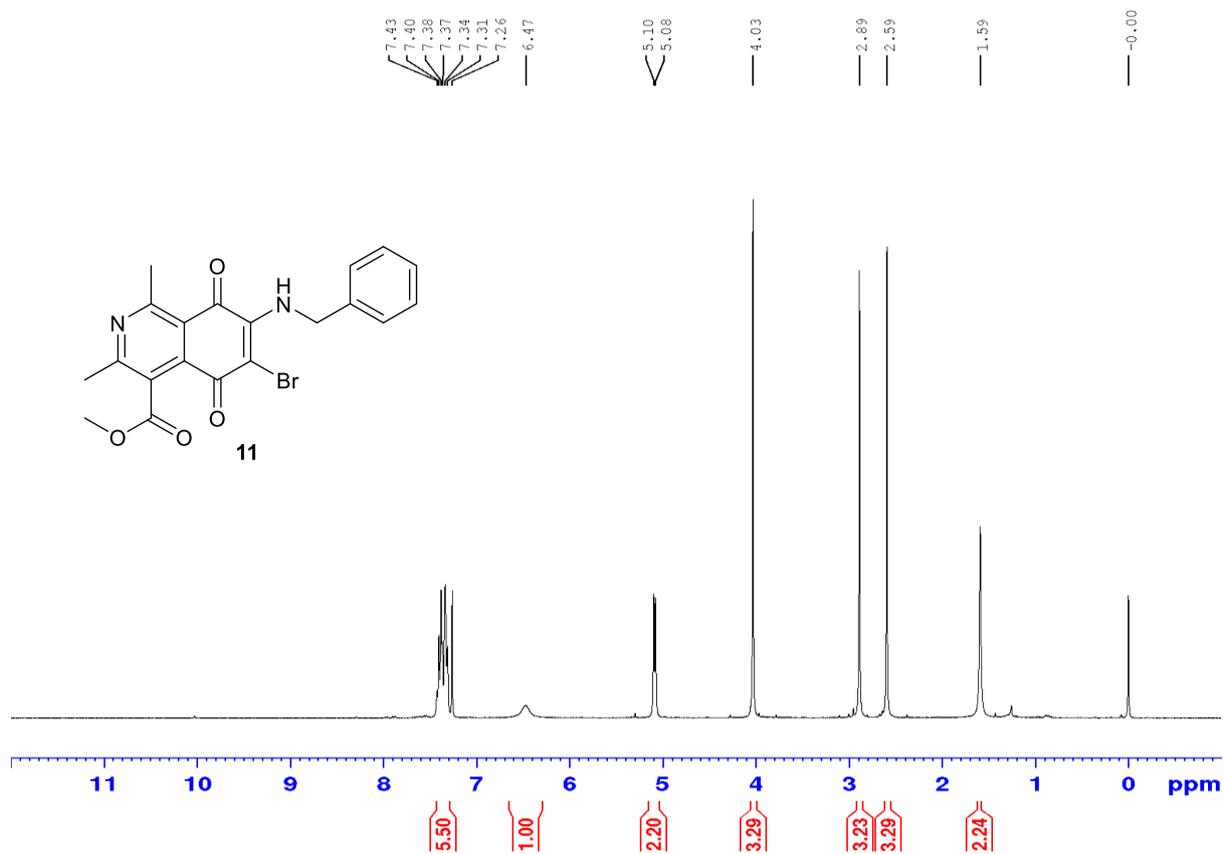
¹H NMR of 10



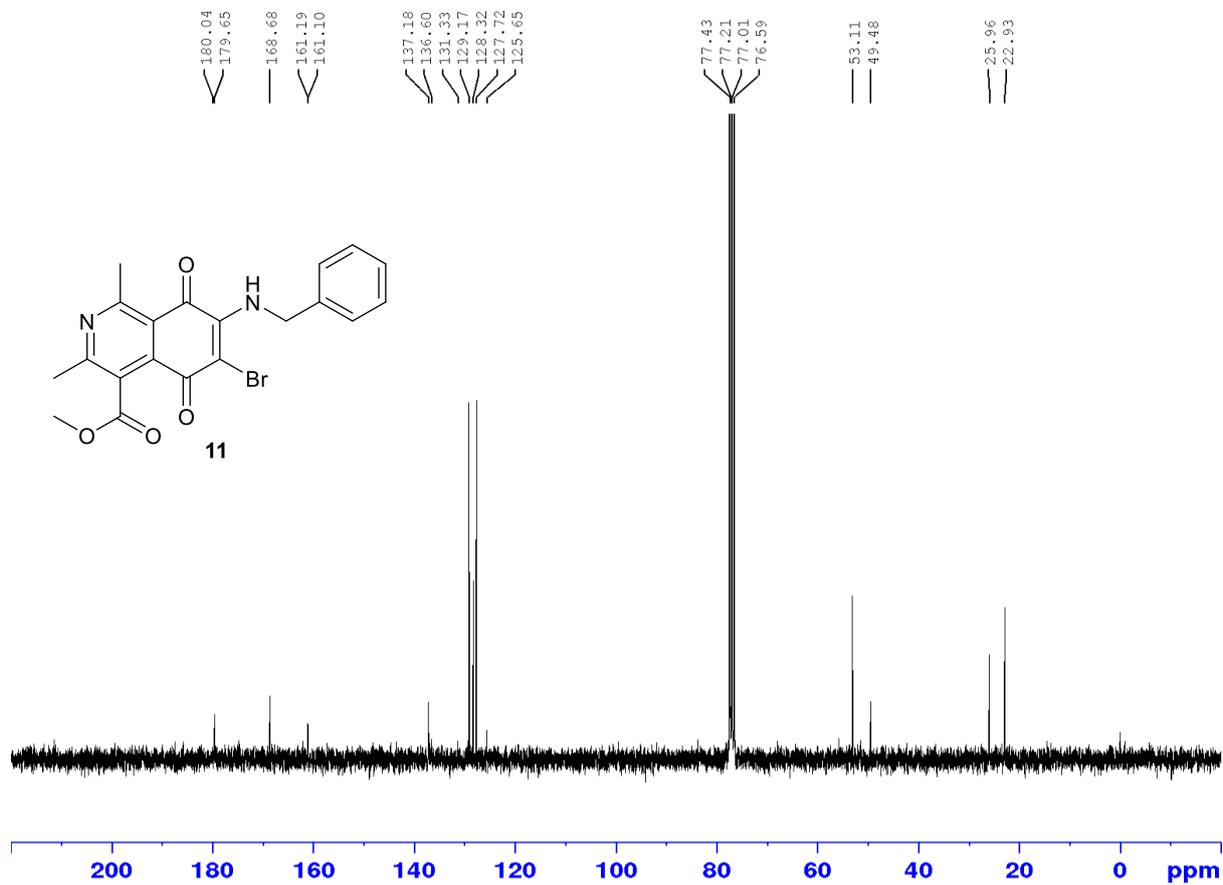
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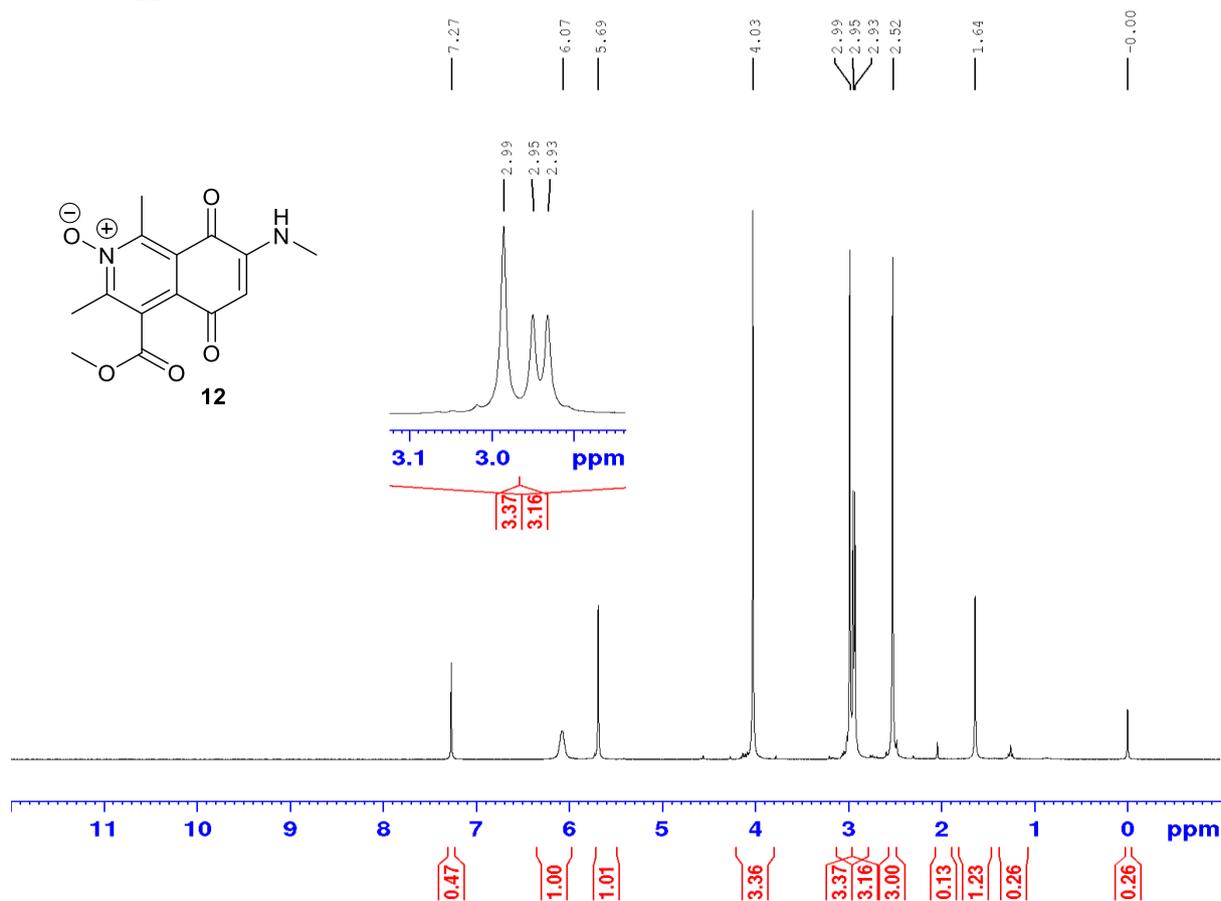
¹H NMR of **11**



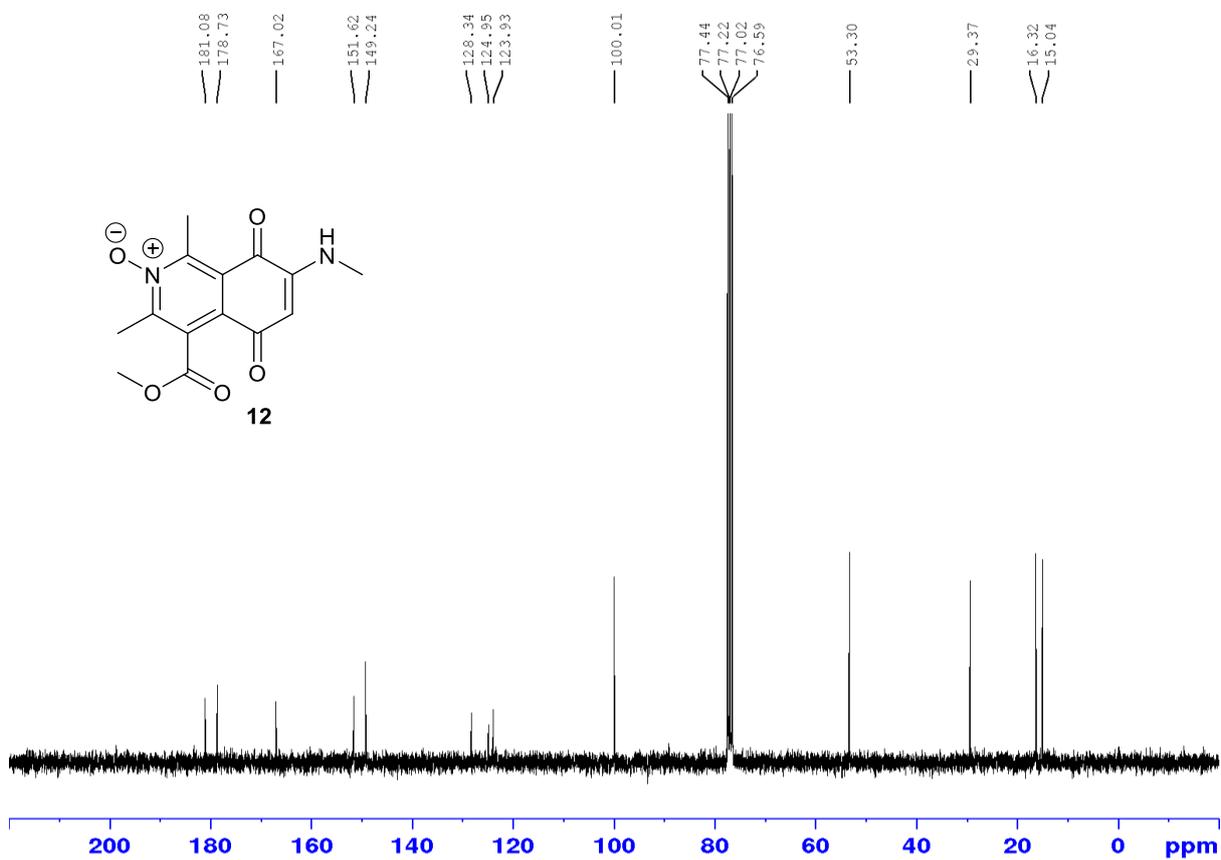
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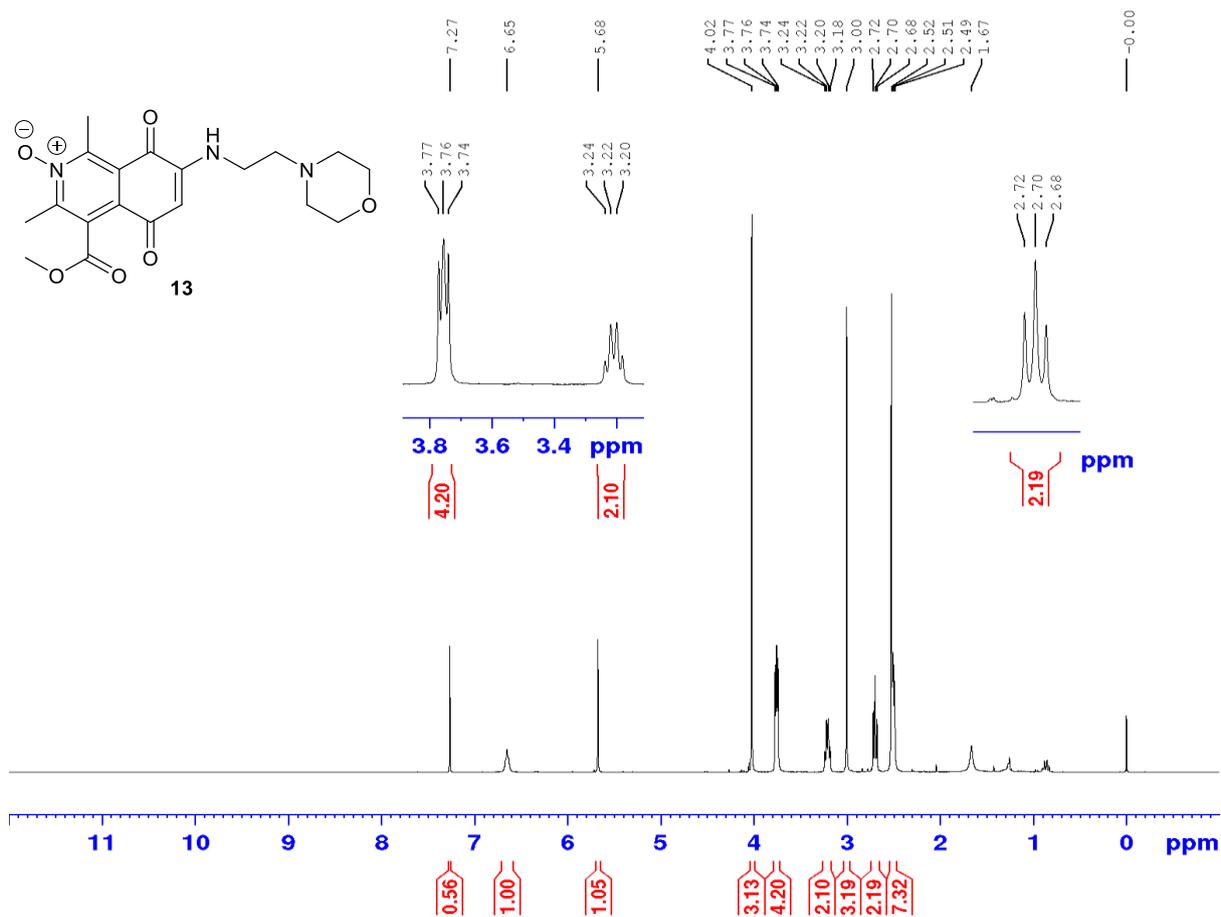
¹H NMR of **12**



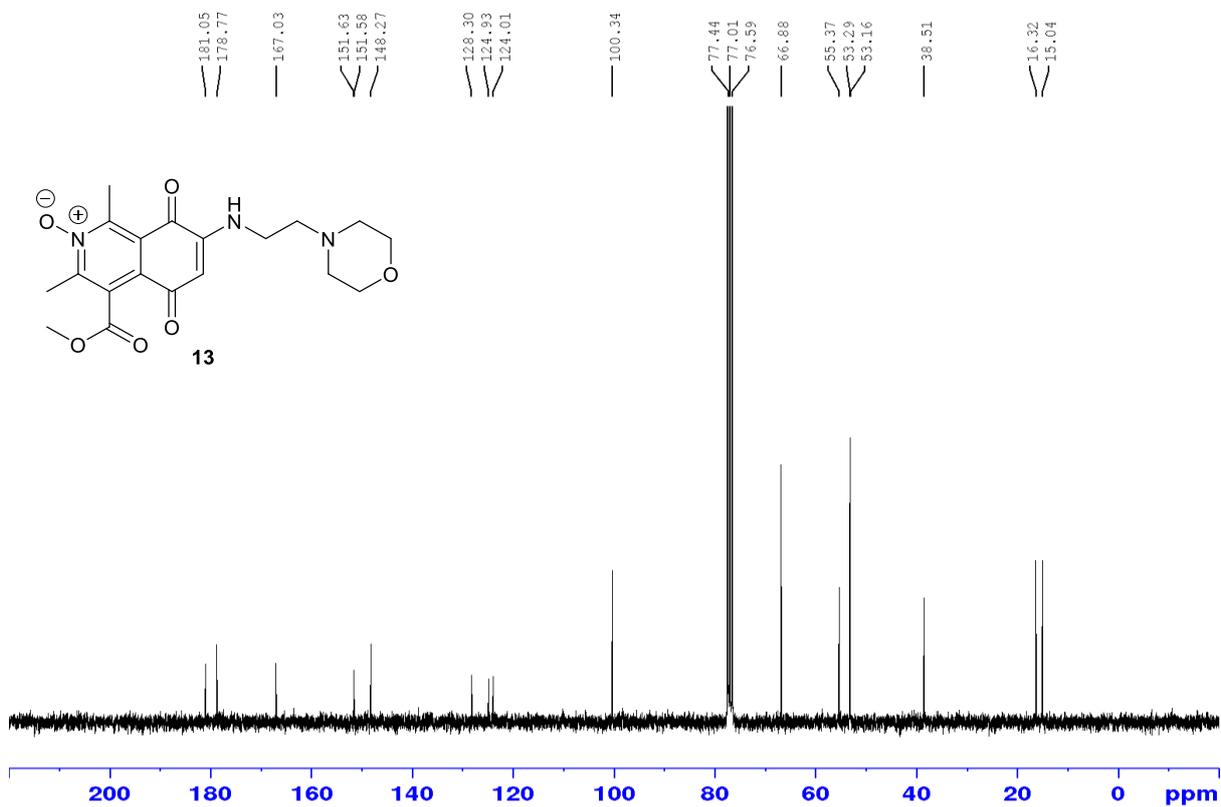
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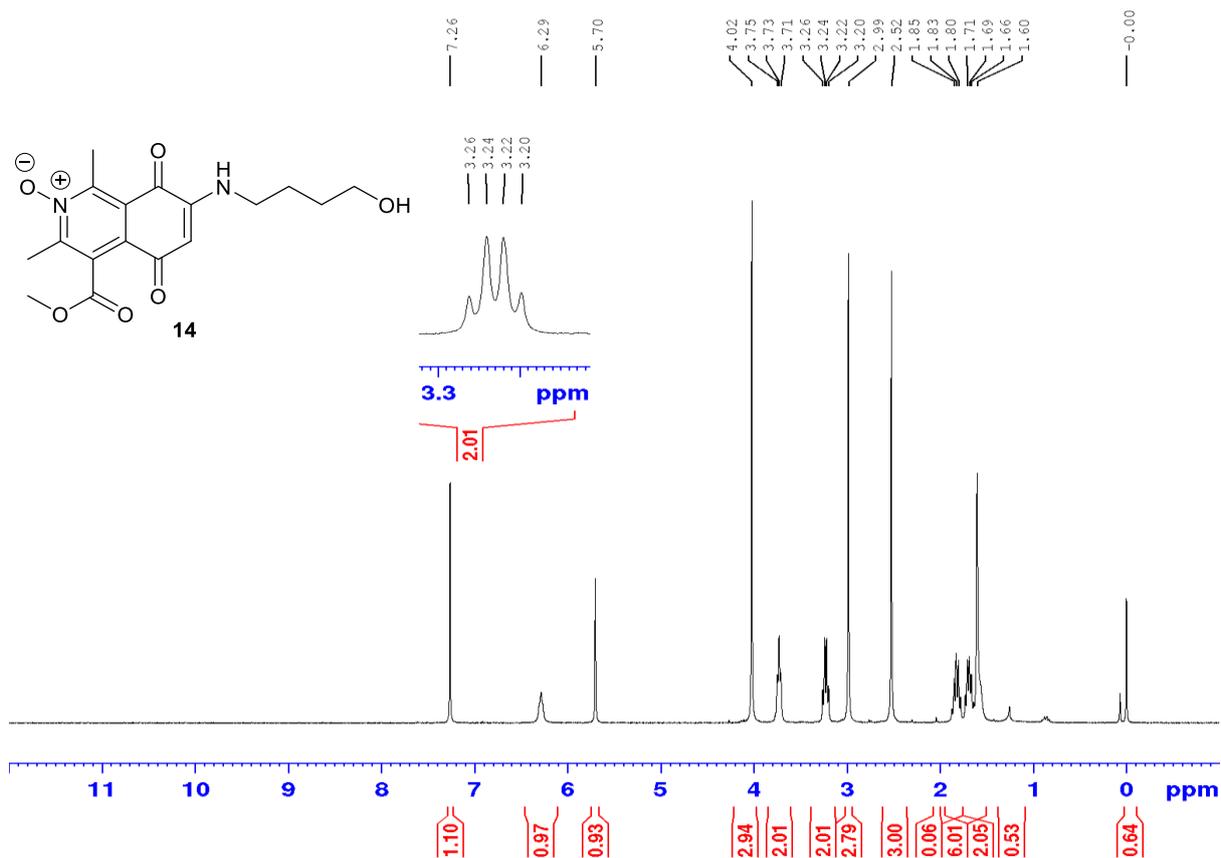
¹H NMR of 13



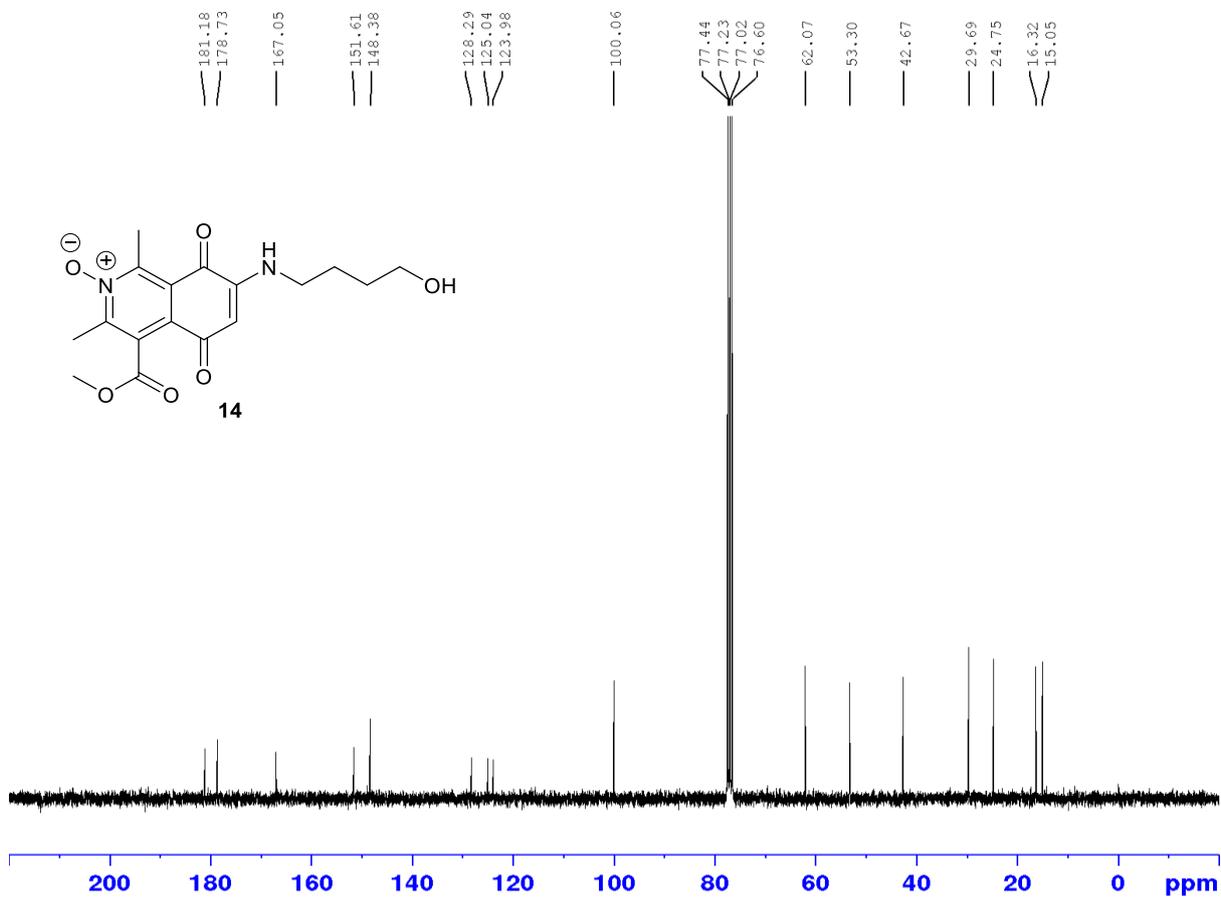
¹³C NMR of 13



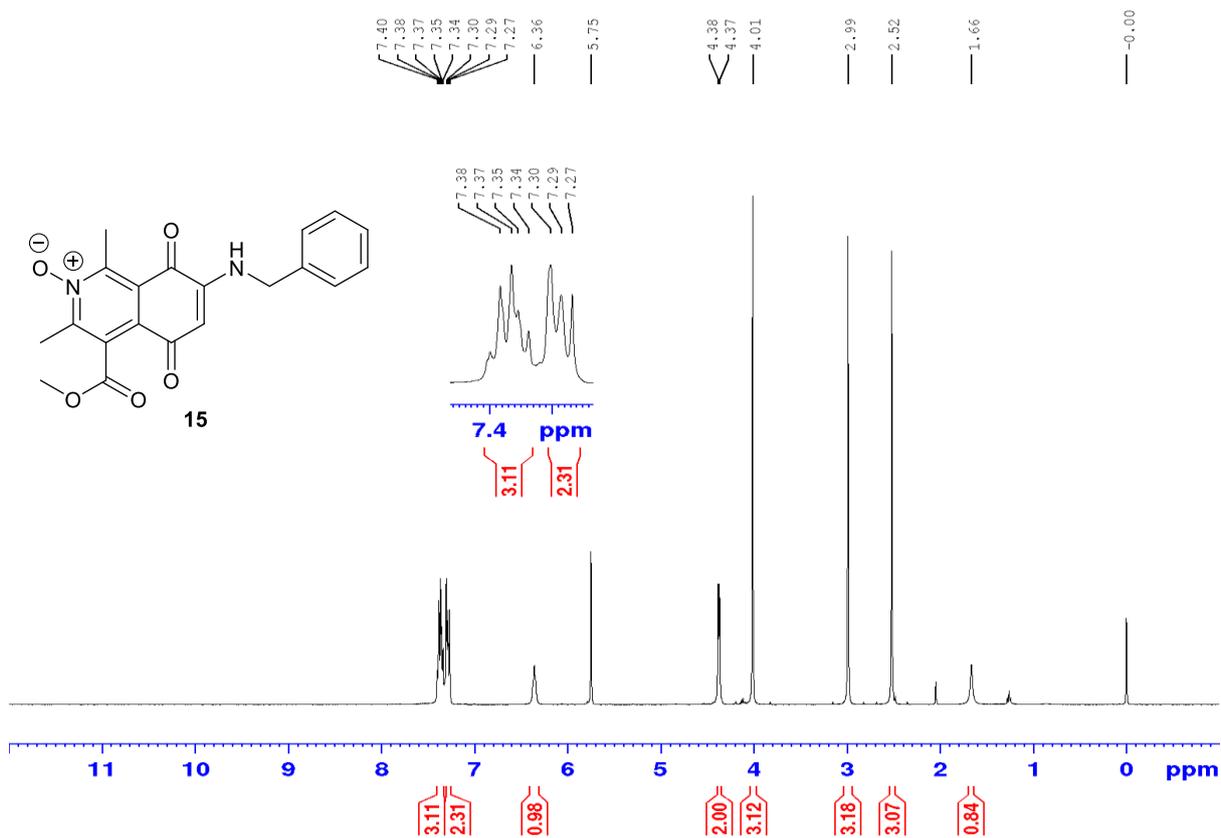
¹H NMR of **14**



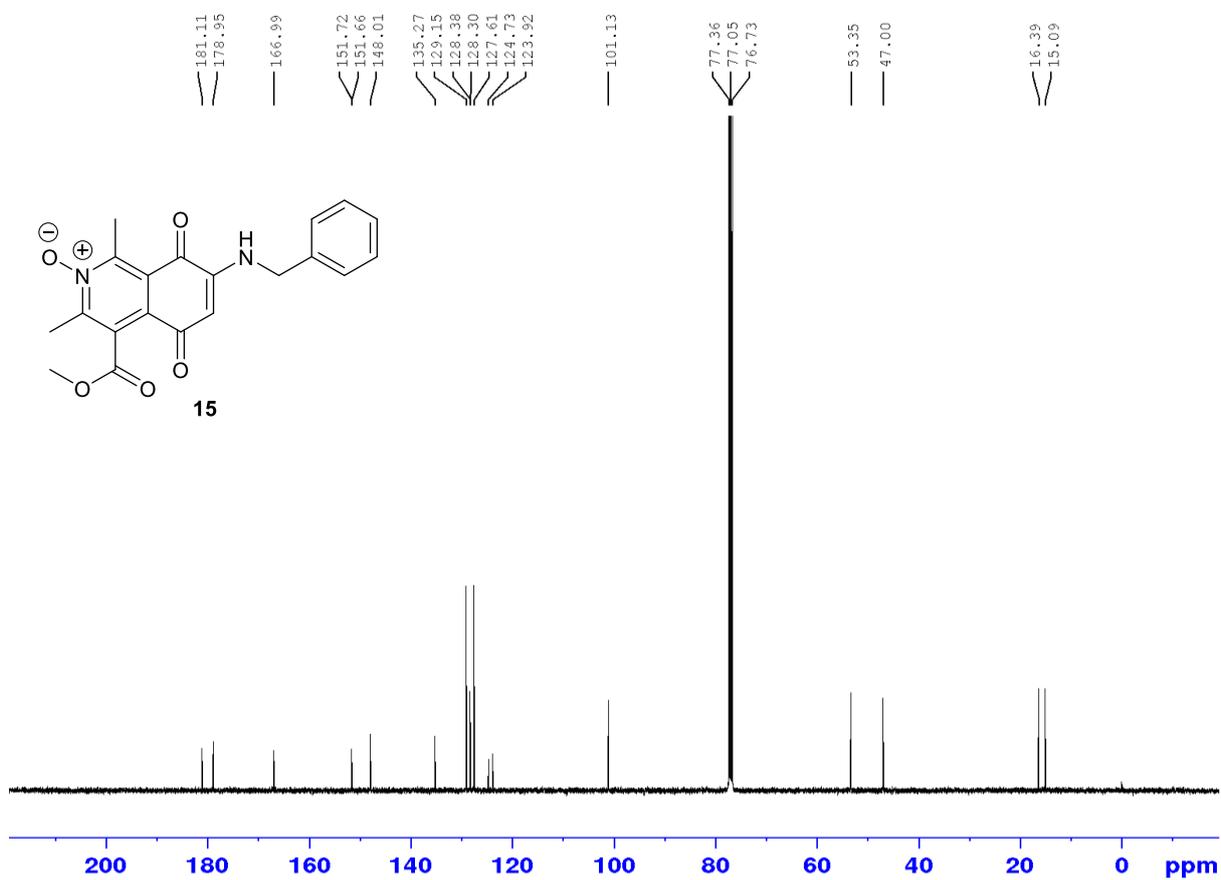
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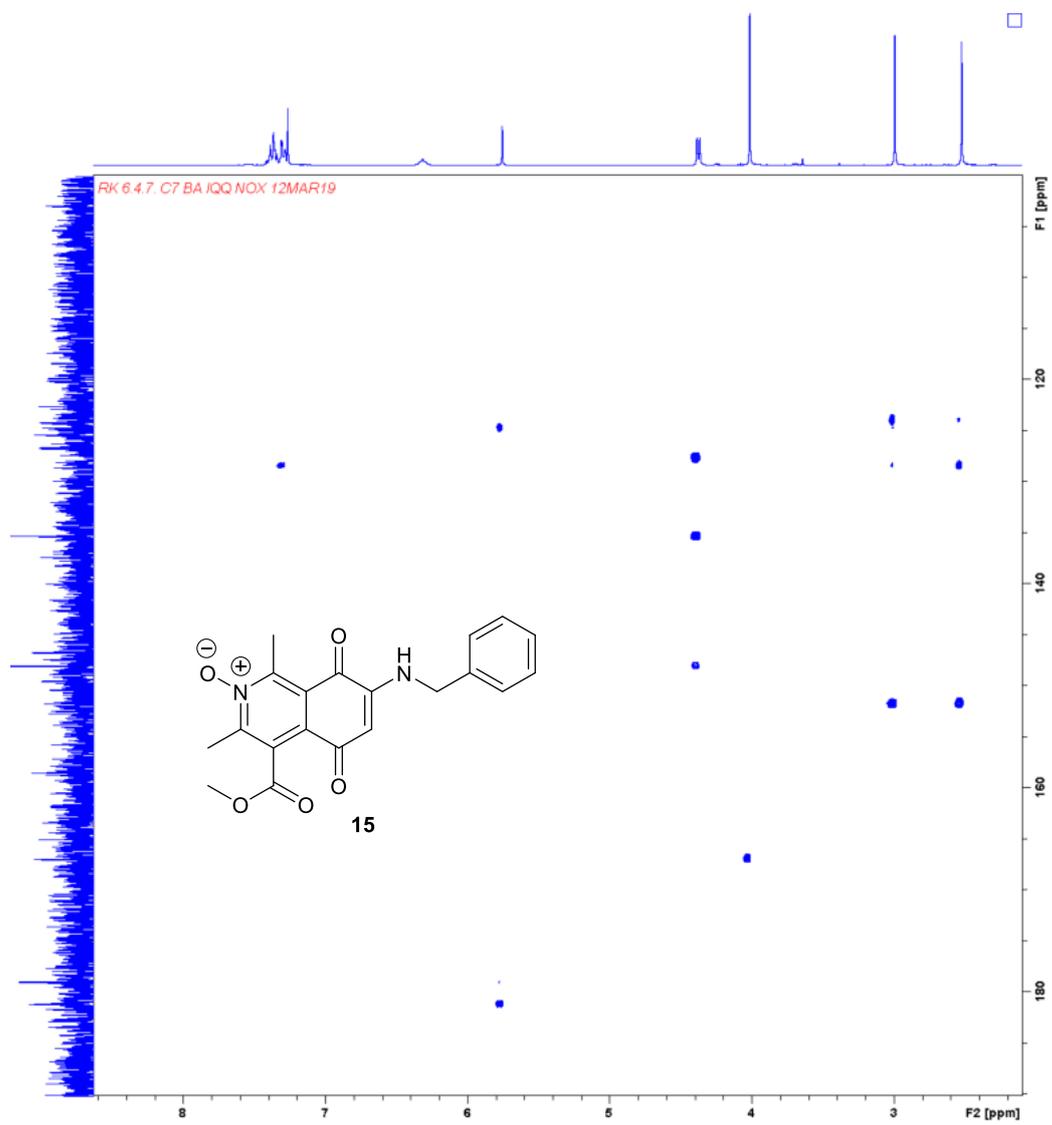
¹H NMR of 15



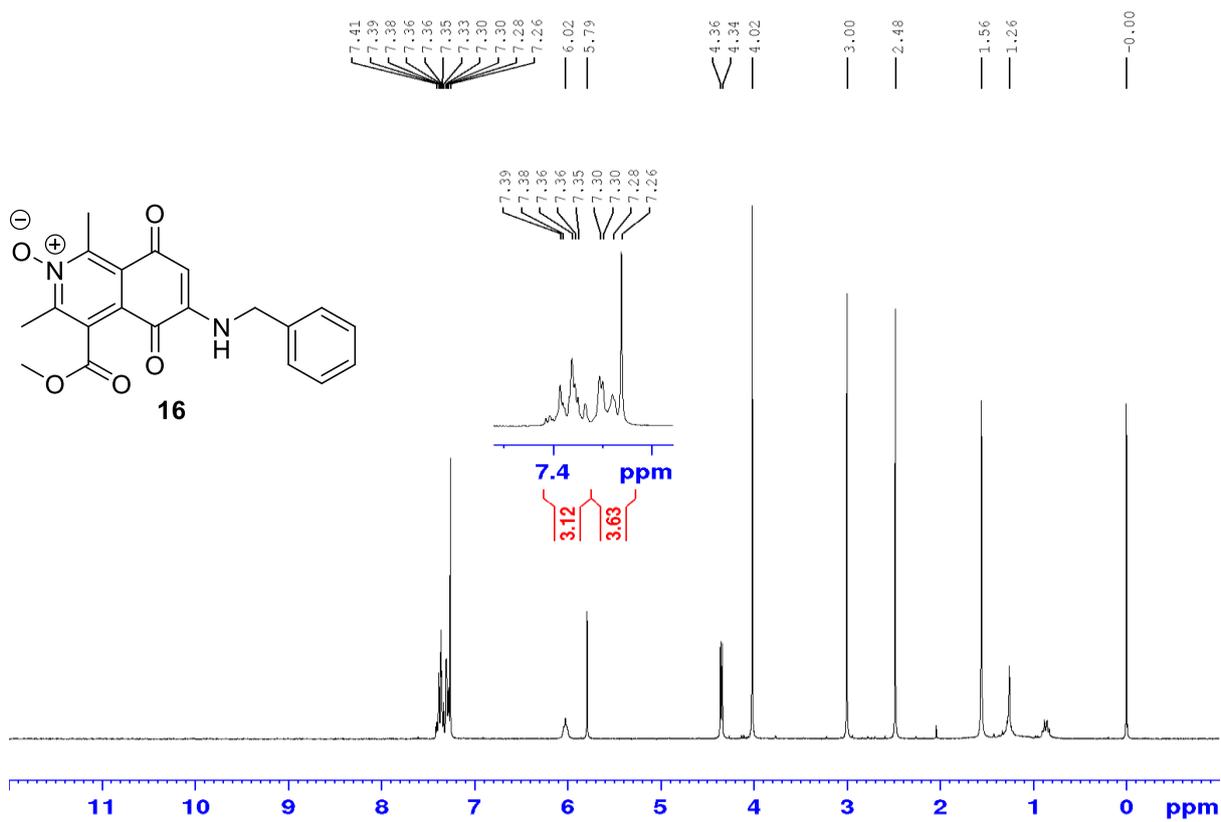
¹³C NMR of 15



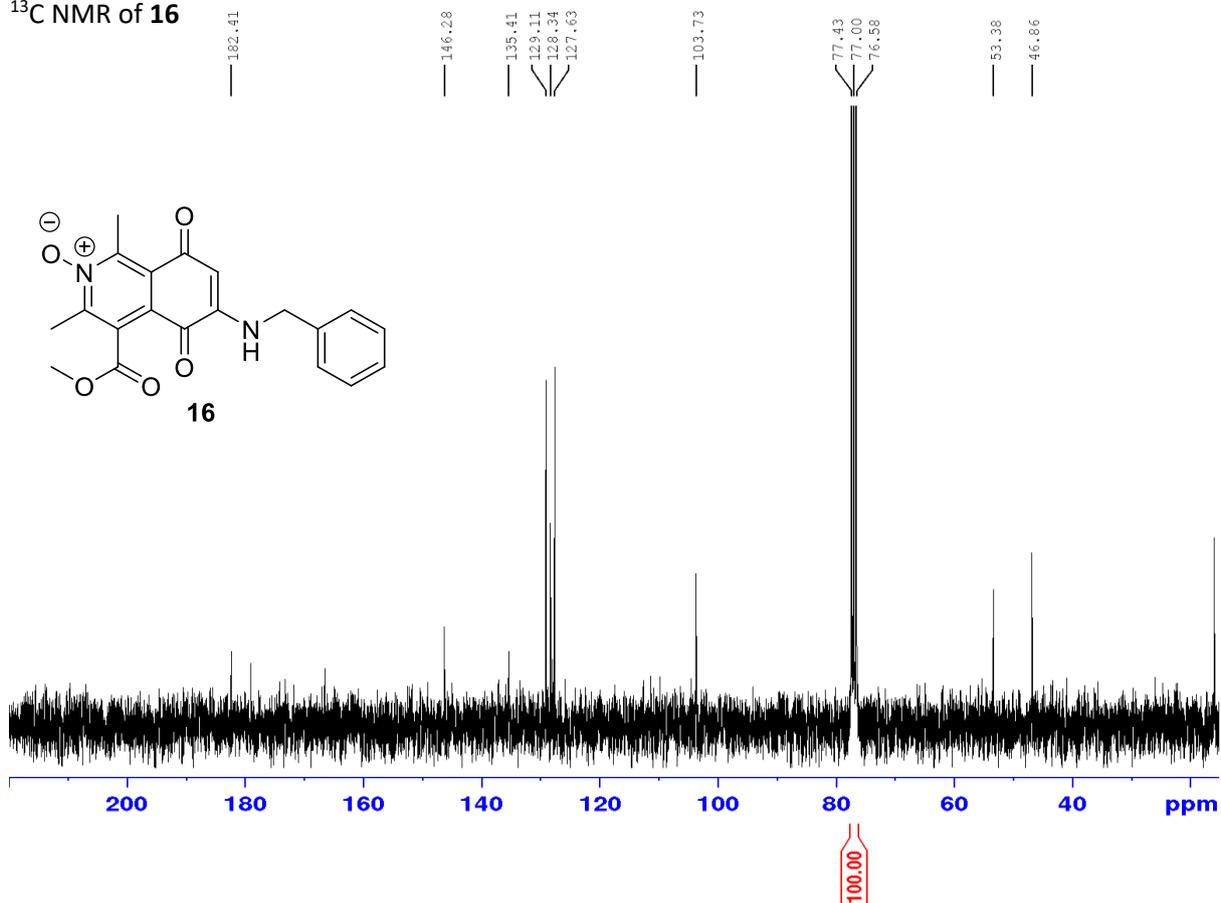
HMBC of 15



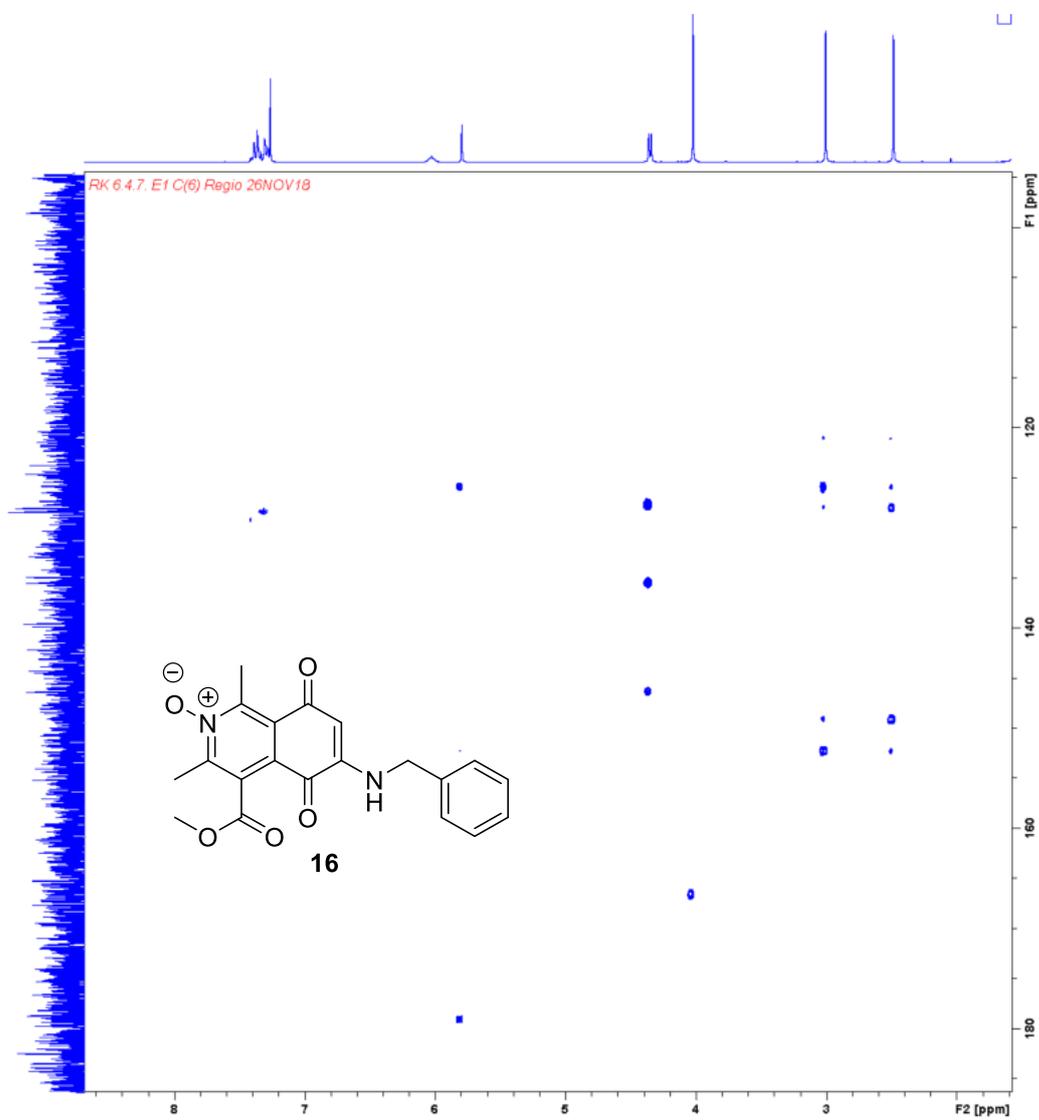
¹H NMR of 16



¹³C NMR of 16

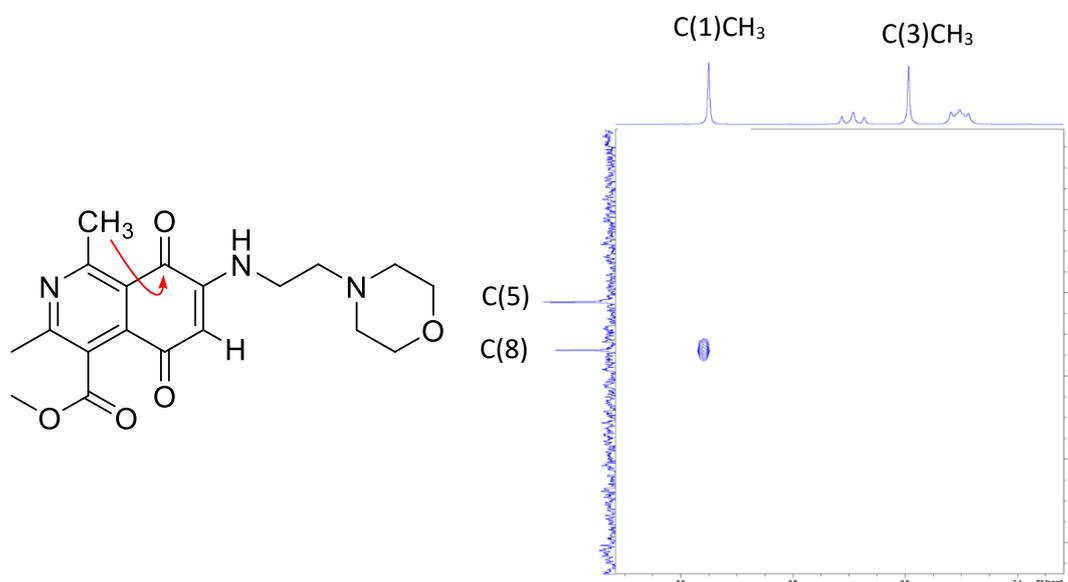


HMBC of 16

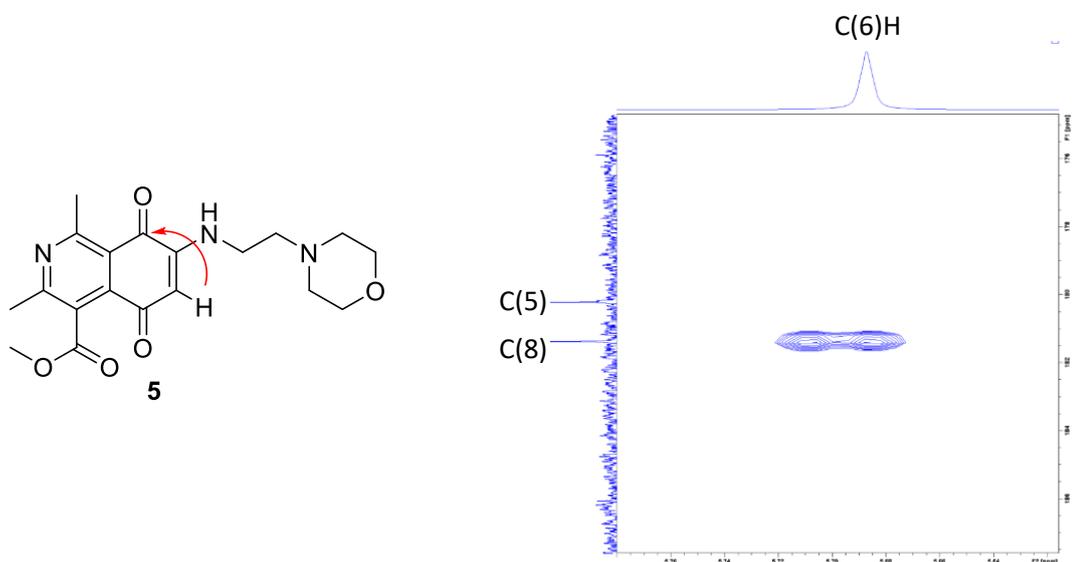


Confirmation of regioisomer assignment of compound 15 and 16

- With respect to morpholino derivative **5** – Crystal structure obtained
- On HMBC analysis, C(1)CH₃ is more downfield and correlated to the C(8) quinone



- C(6)H correlates to C(8) quinone confirmed using X-ray single crystal and HMBC



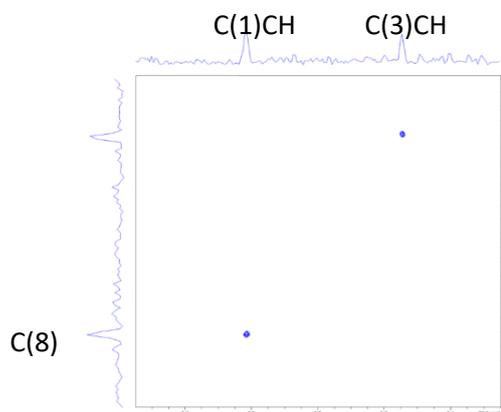
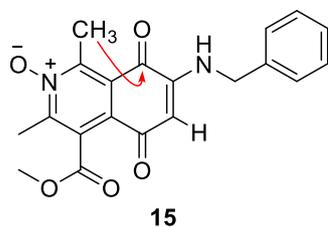
For the benzylamine isoquinolinequinone N-oxides **15** and **16**:

C(7) Regioisomer **15** - Correlation of C(6)H with 181.0 ppm, which is the C(8) carbonyl

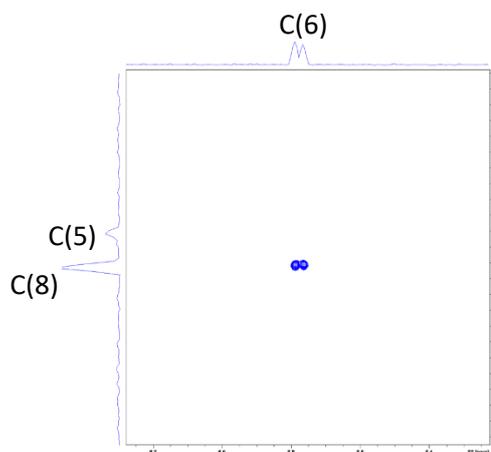
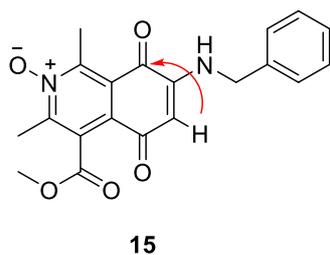
C(6) Regioisomer **16** - Correlation of C(7)H with 179.1 ppm, which is the C(5) carbonyl

C(7) Regioisomer 15

- Like morpholino derivative 5, C(1)CH₃ correlates to C(8) carbonyl

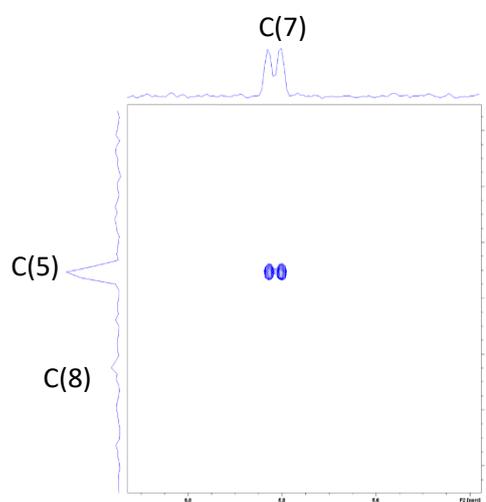
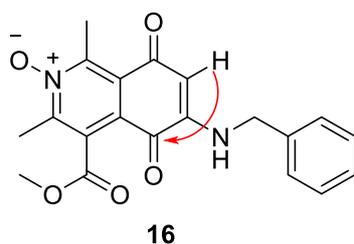


- C(6)H also correlates to the C(8) carbonyl carbon



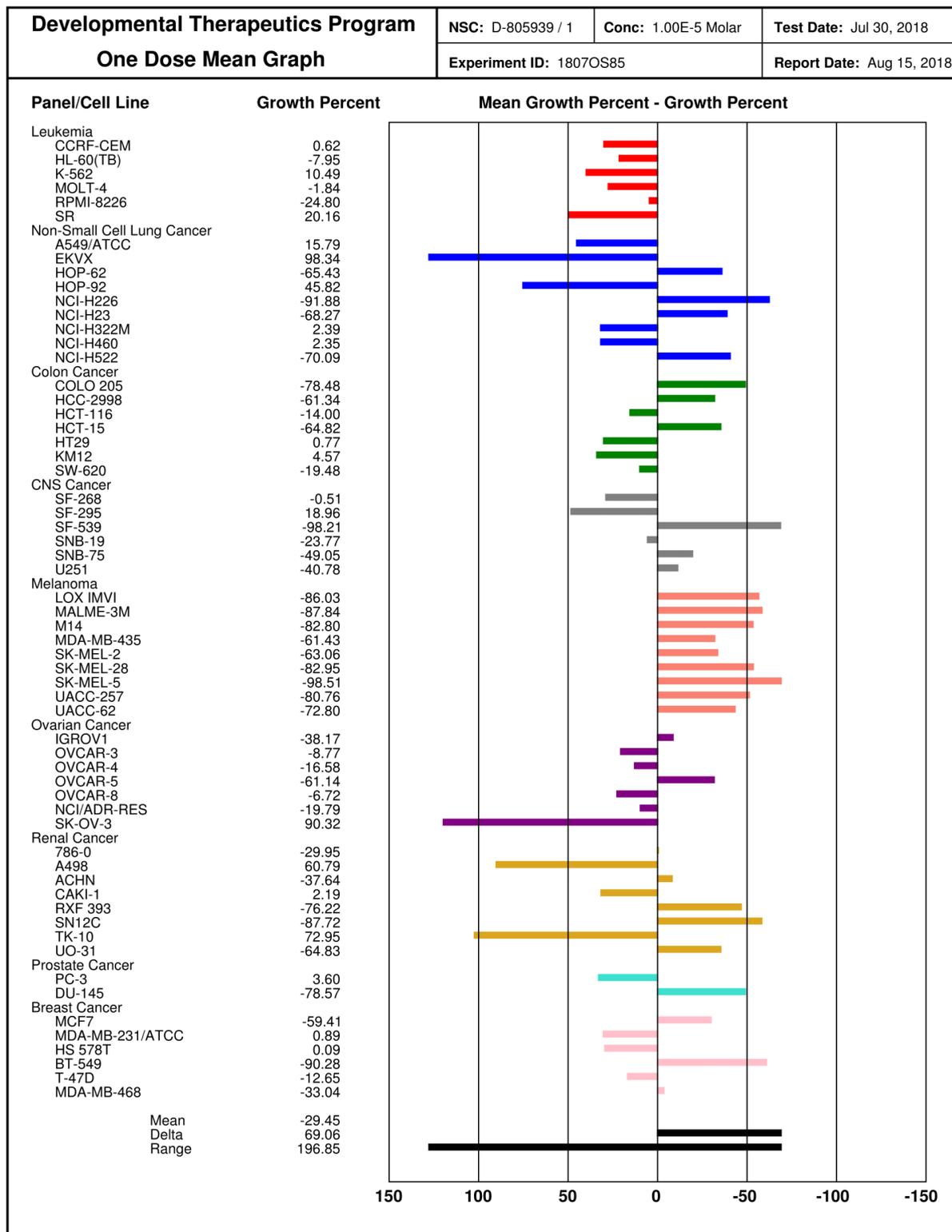
C(6) Regioisomer 16

- C(7)H correlates to the C(5) carbonyl carbon

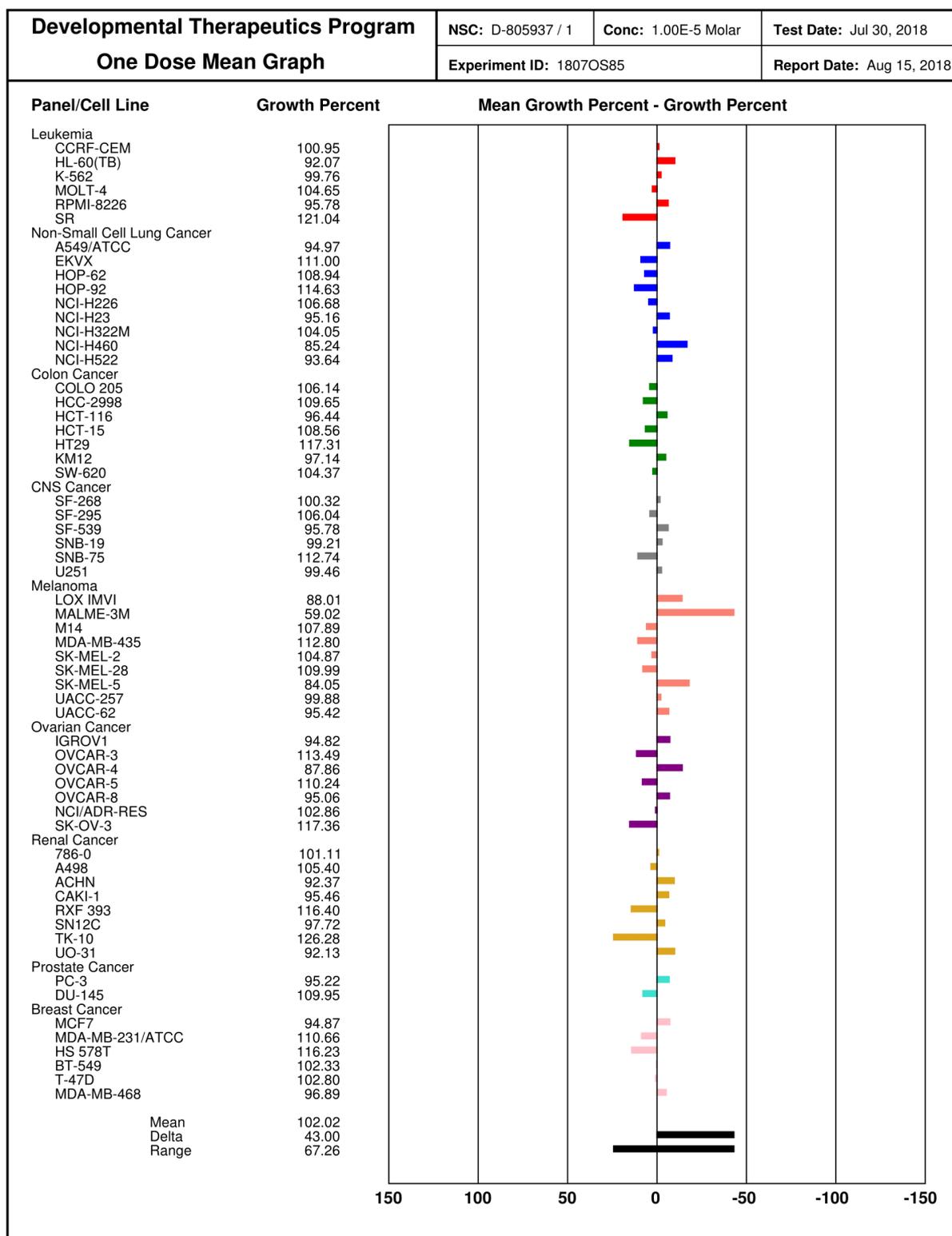


NCI60 One dose Screen

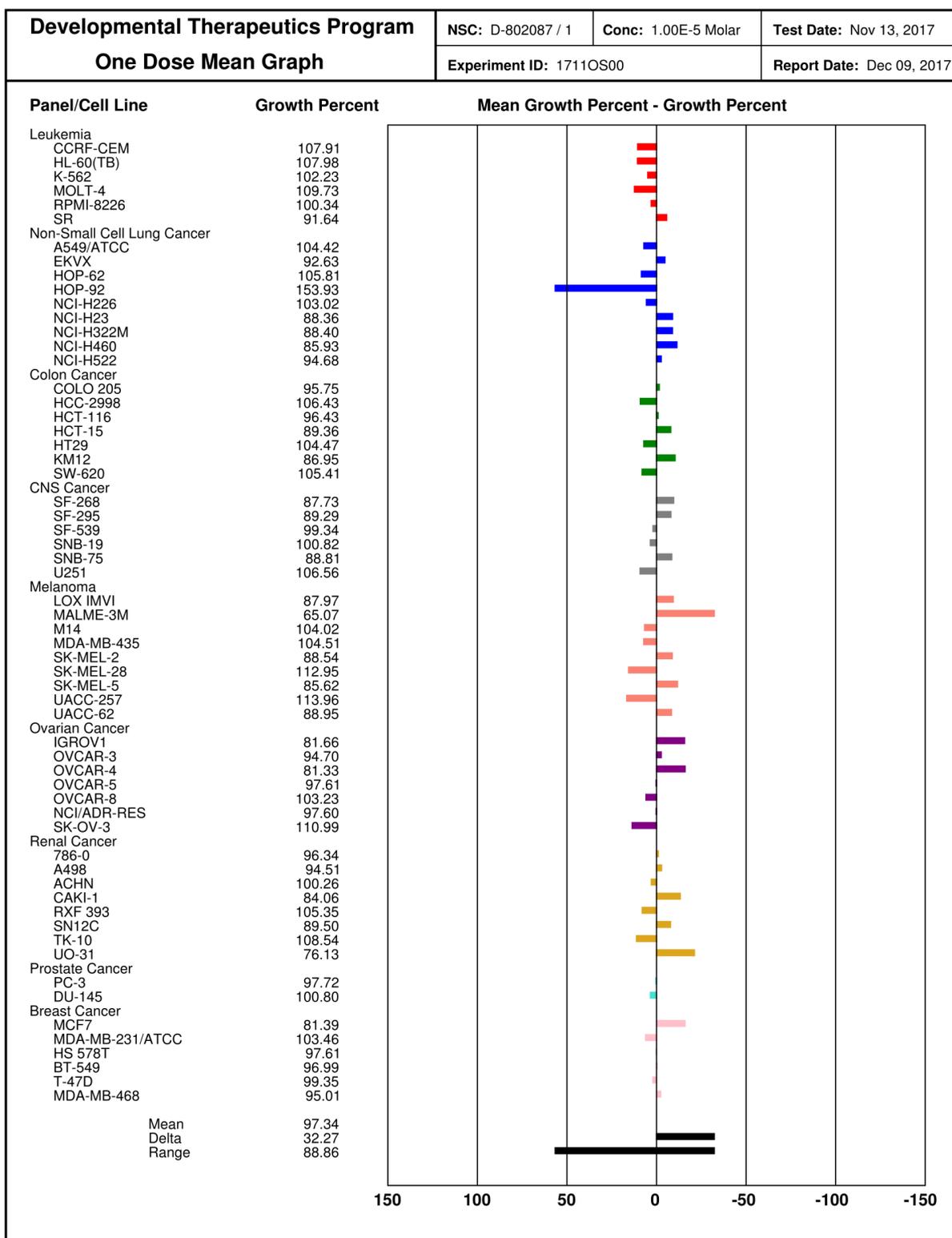
Compound 3



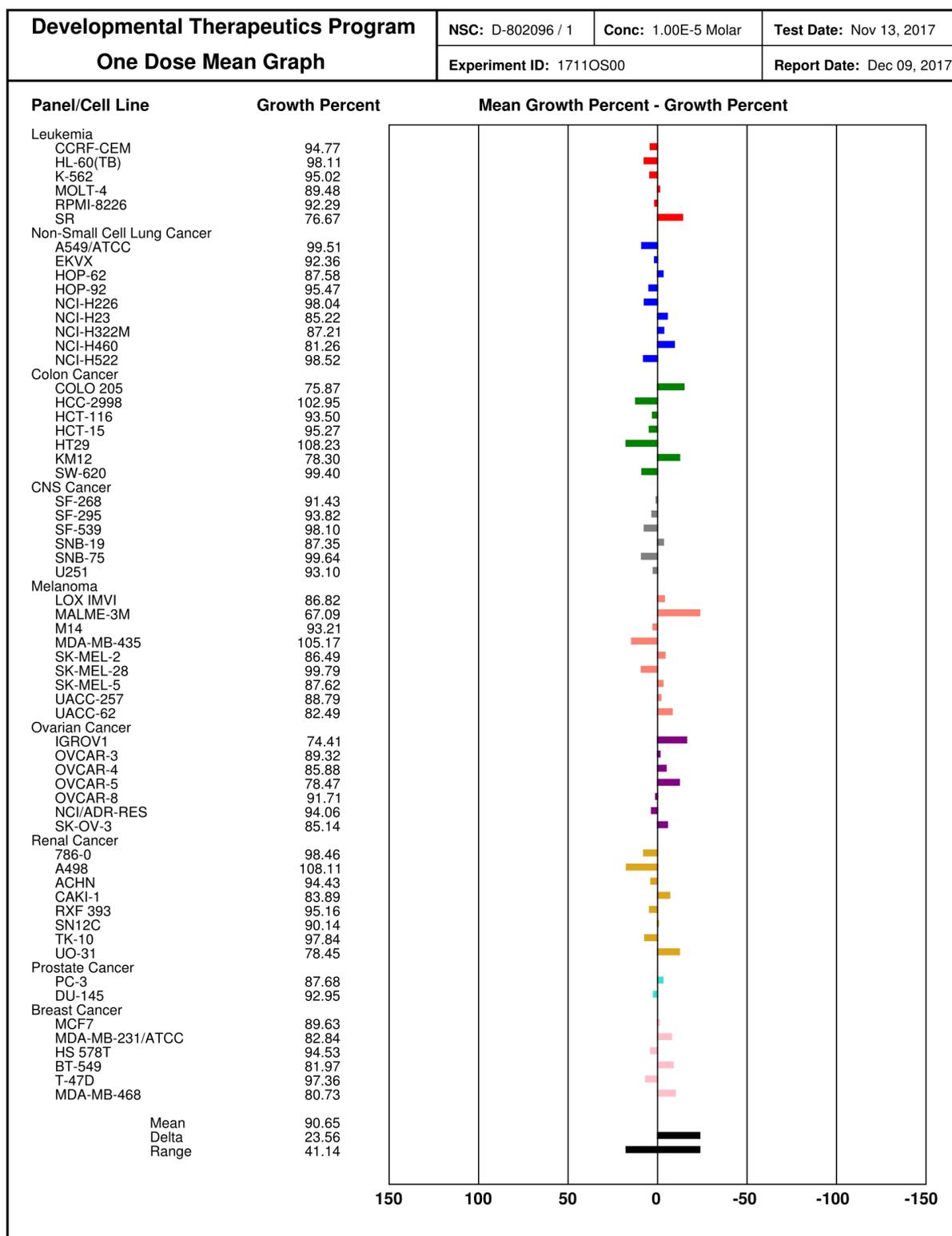
Compound 4



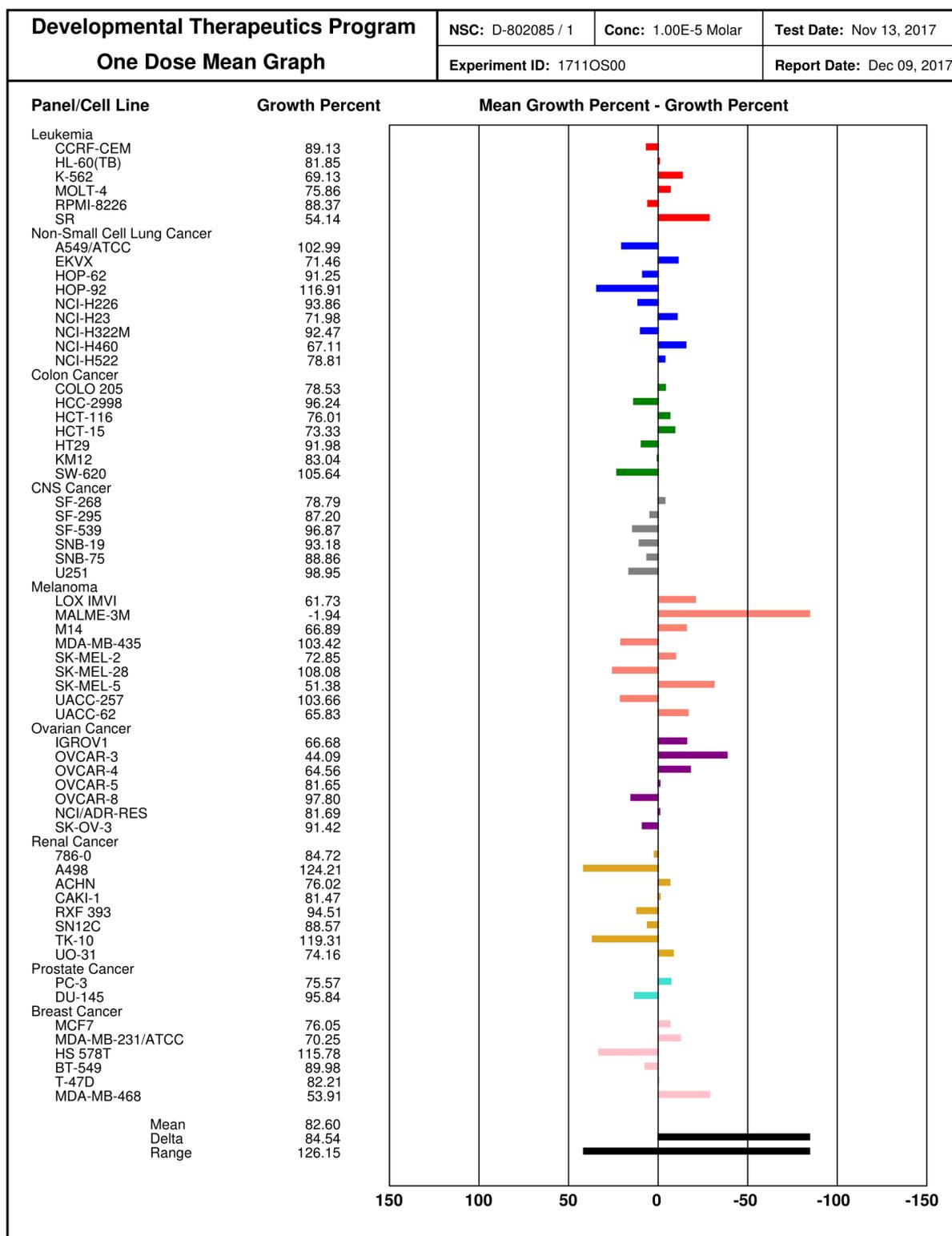
Compound 5



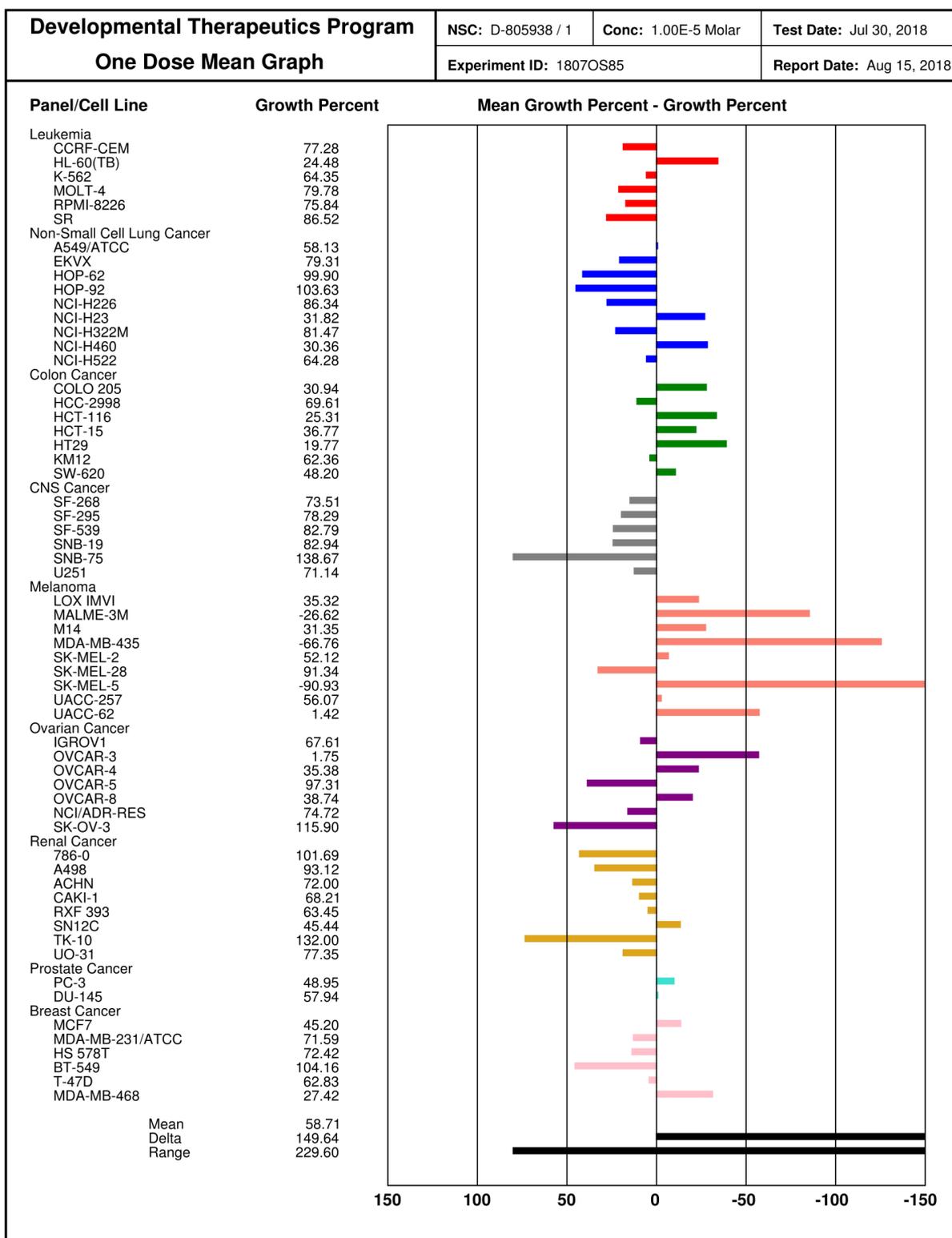
Compound 6



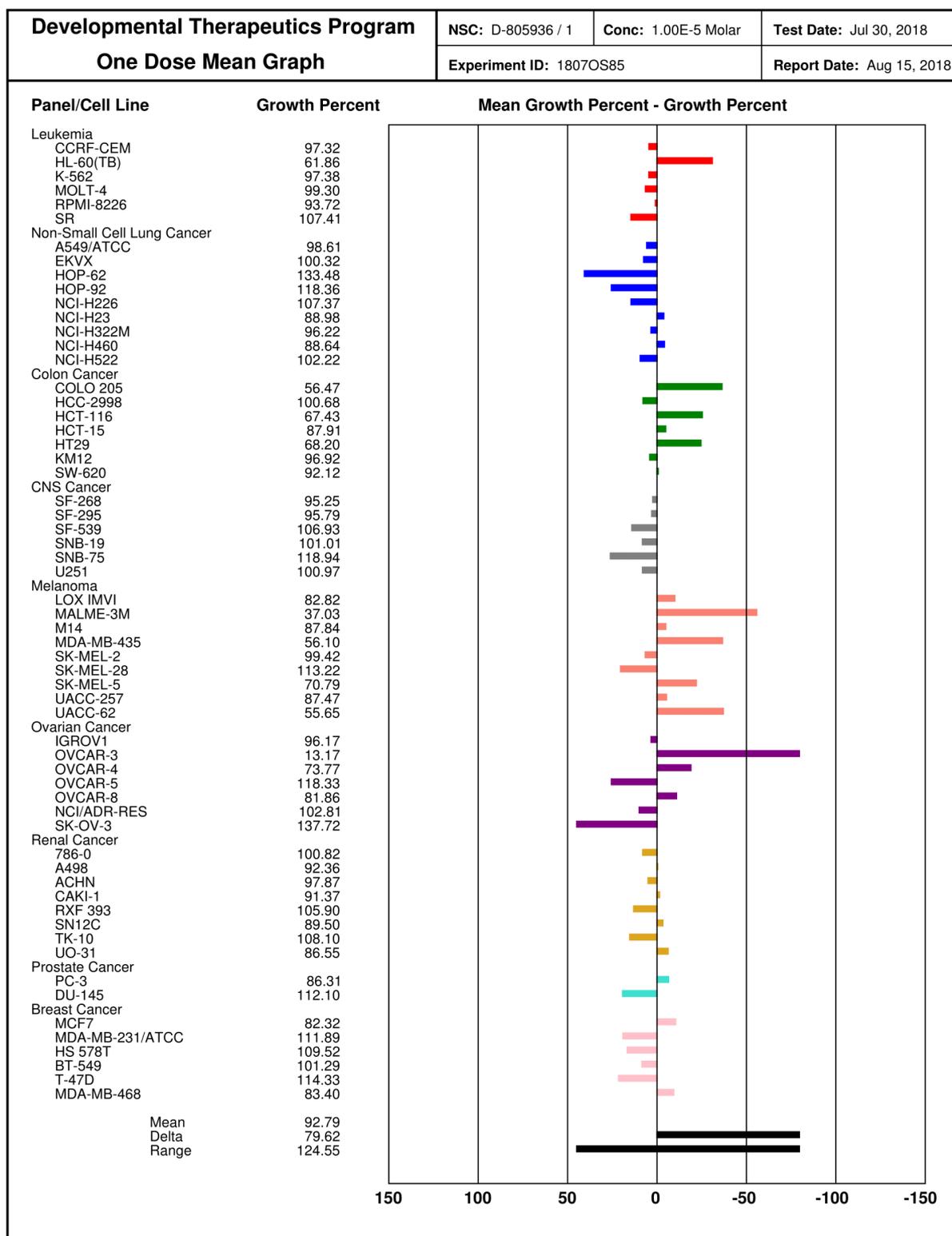
Compound 7



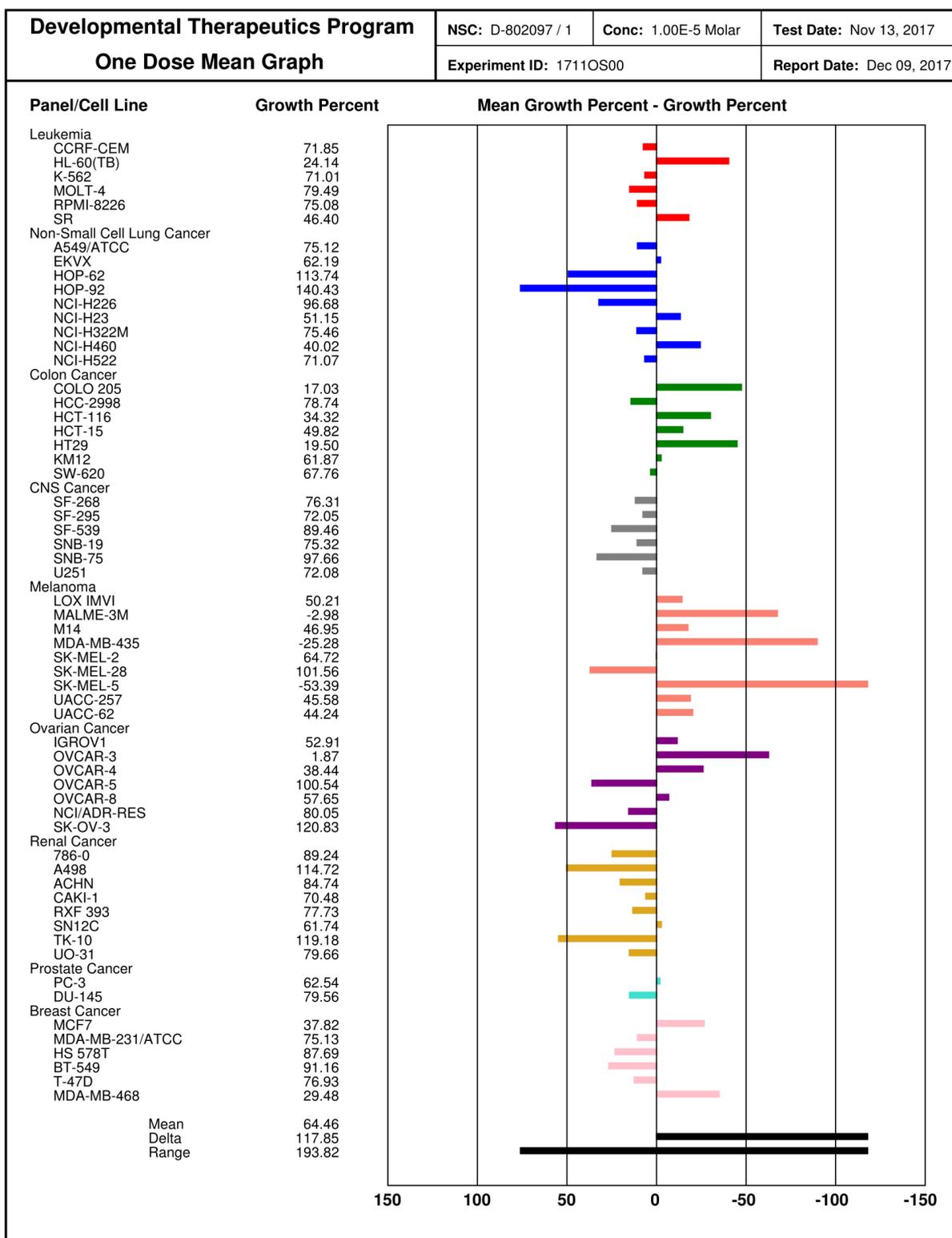
Compound 8



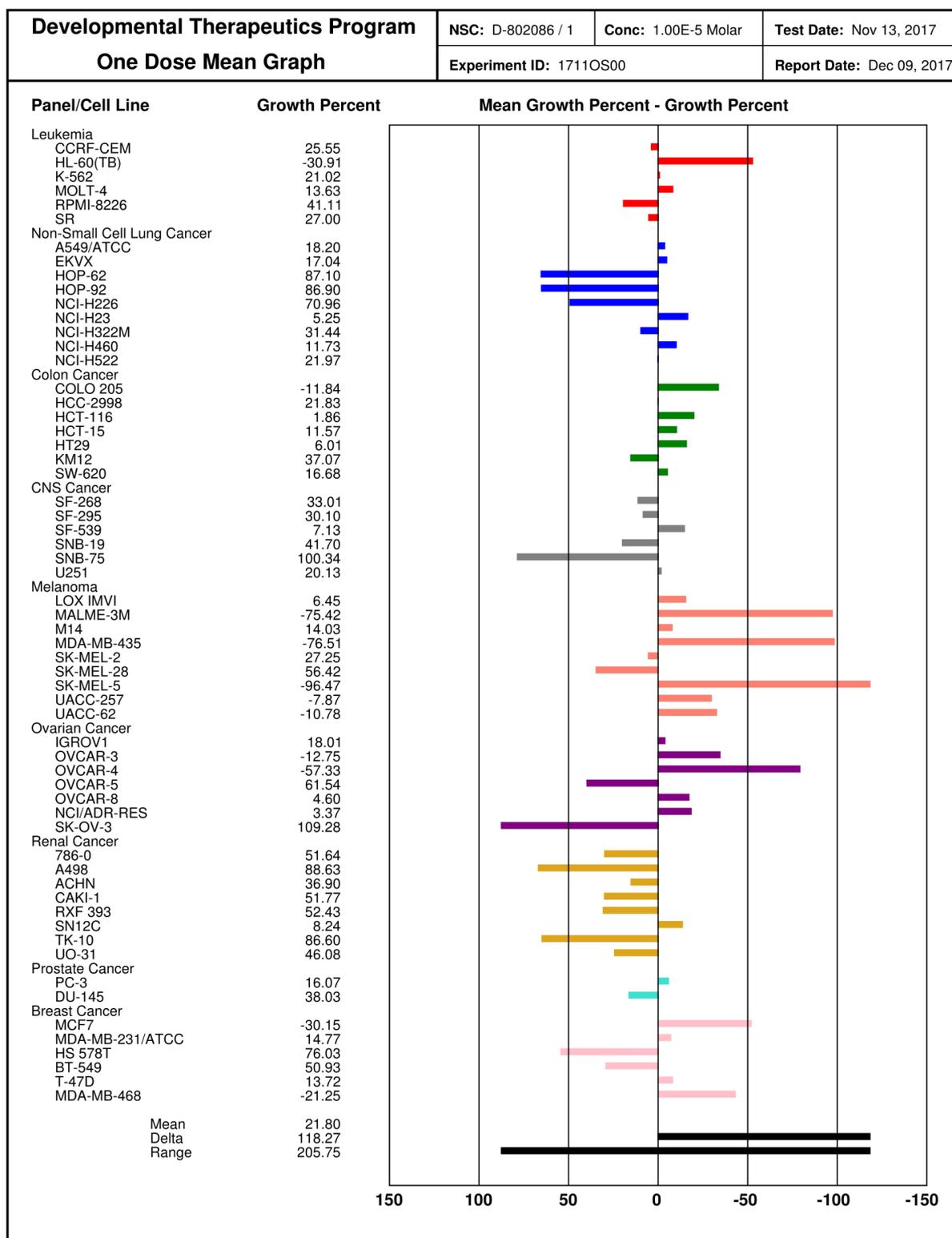
Compound 9



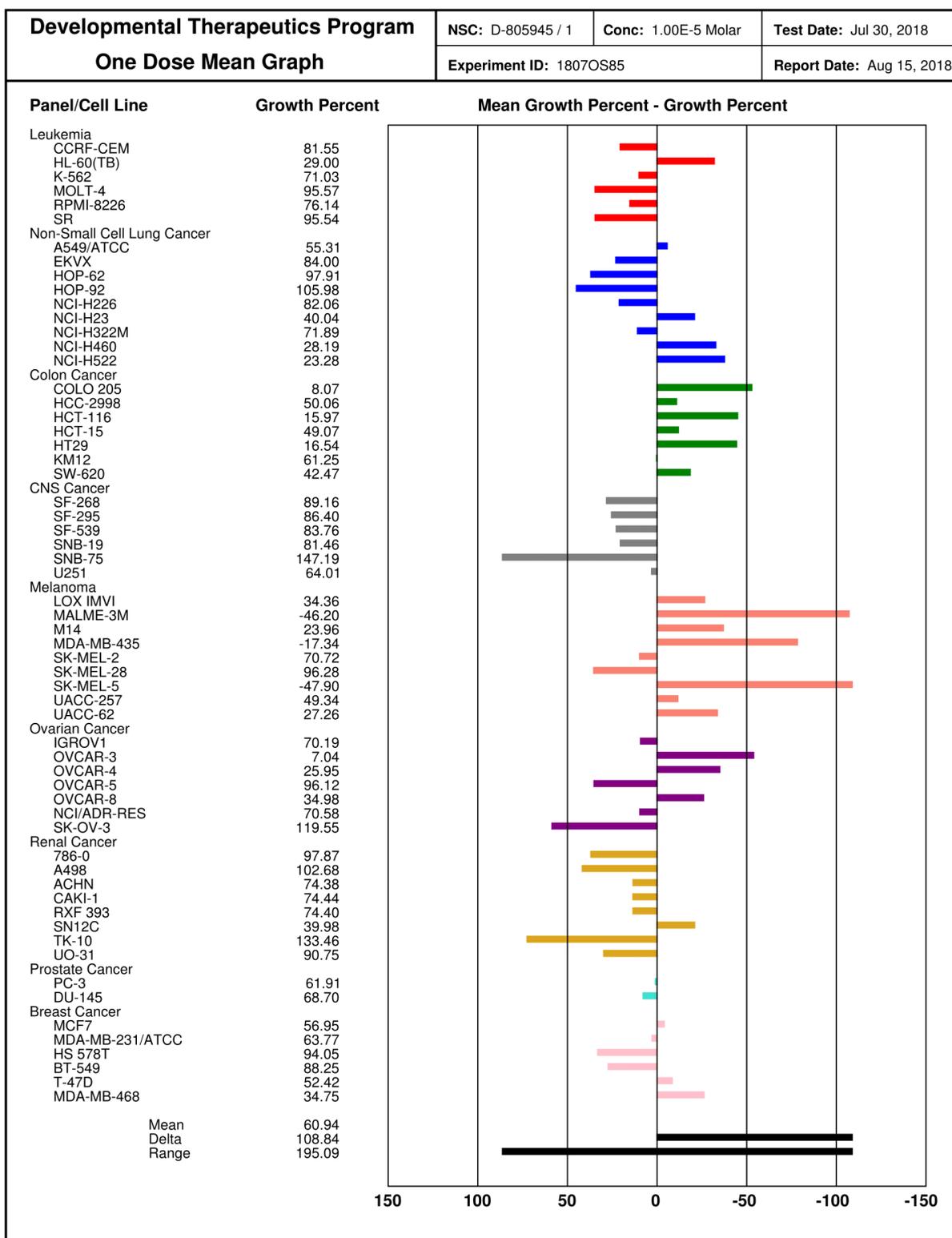
Compound 10



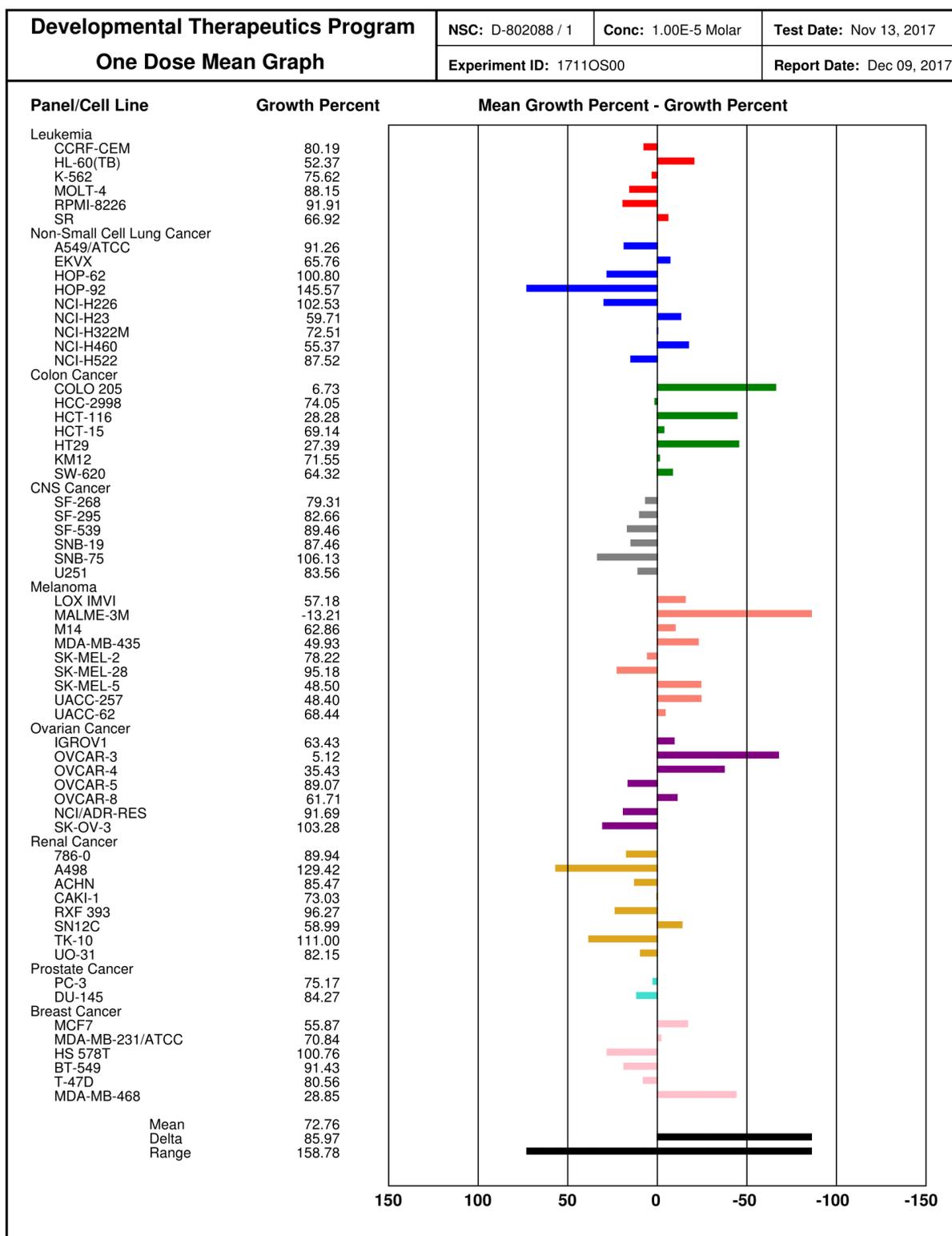
Compound 11



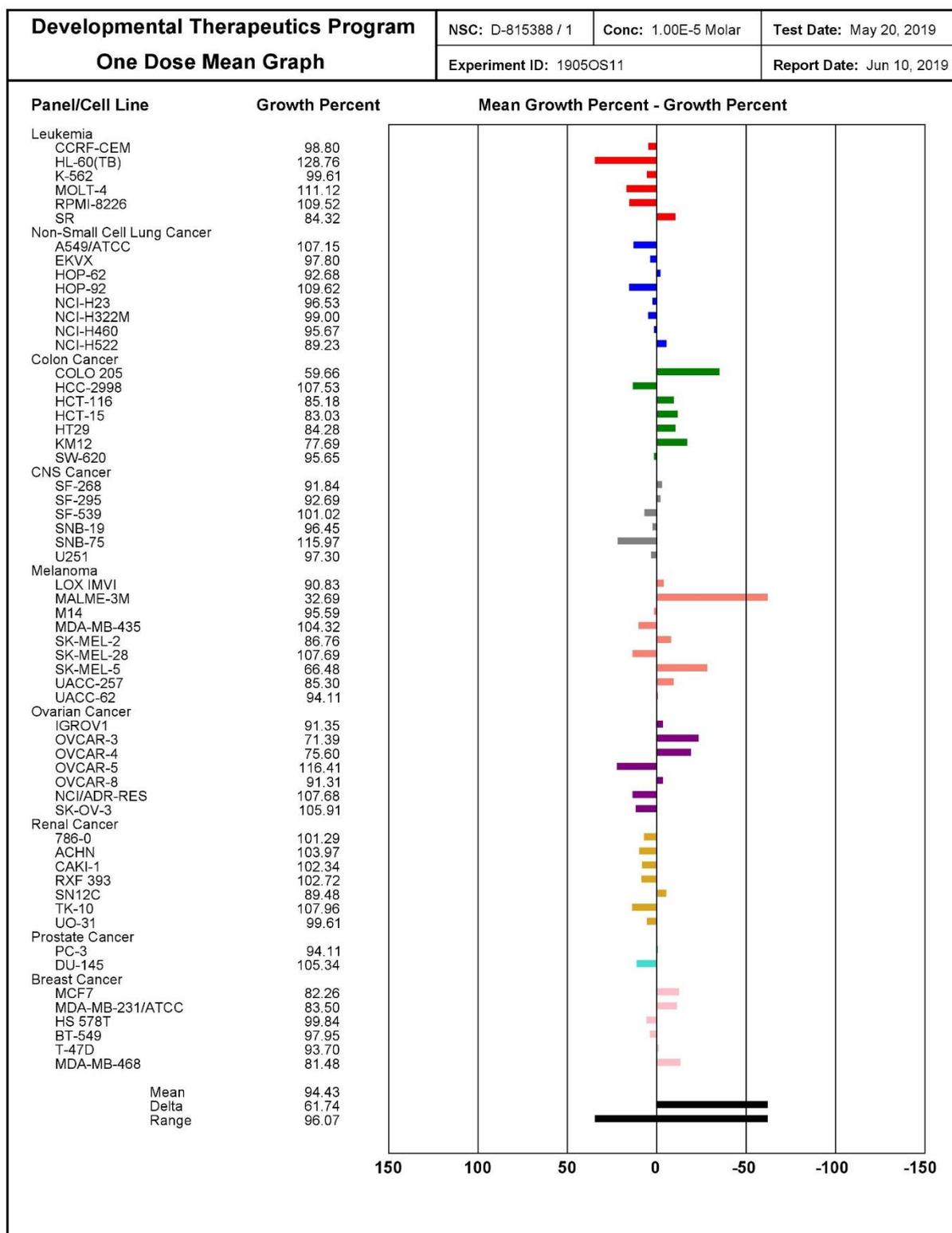
Compound 12



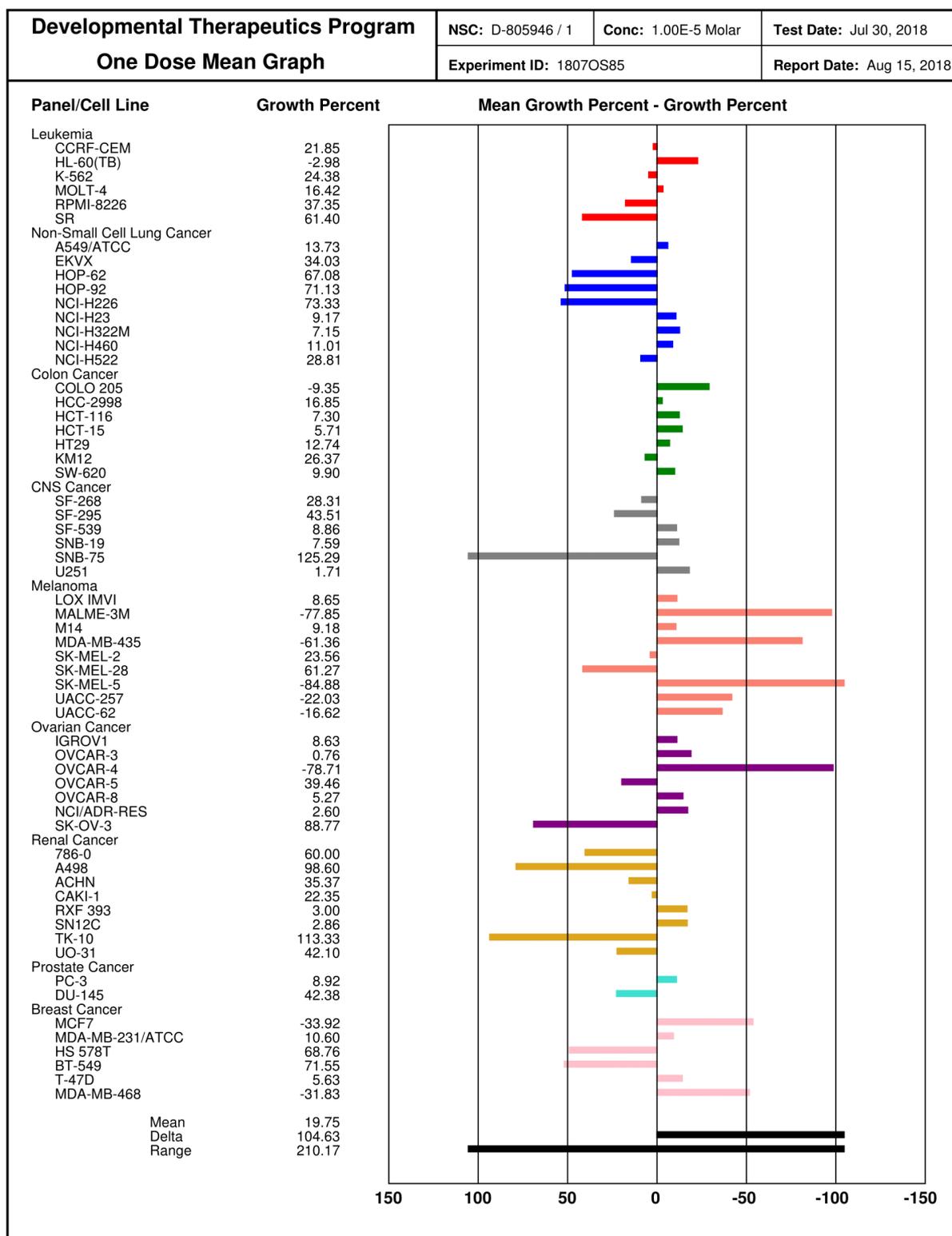
Compound 13



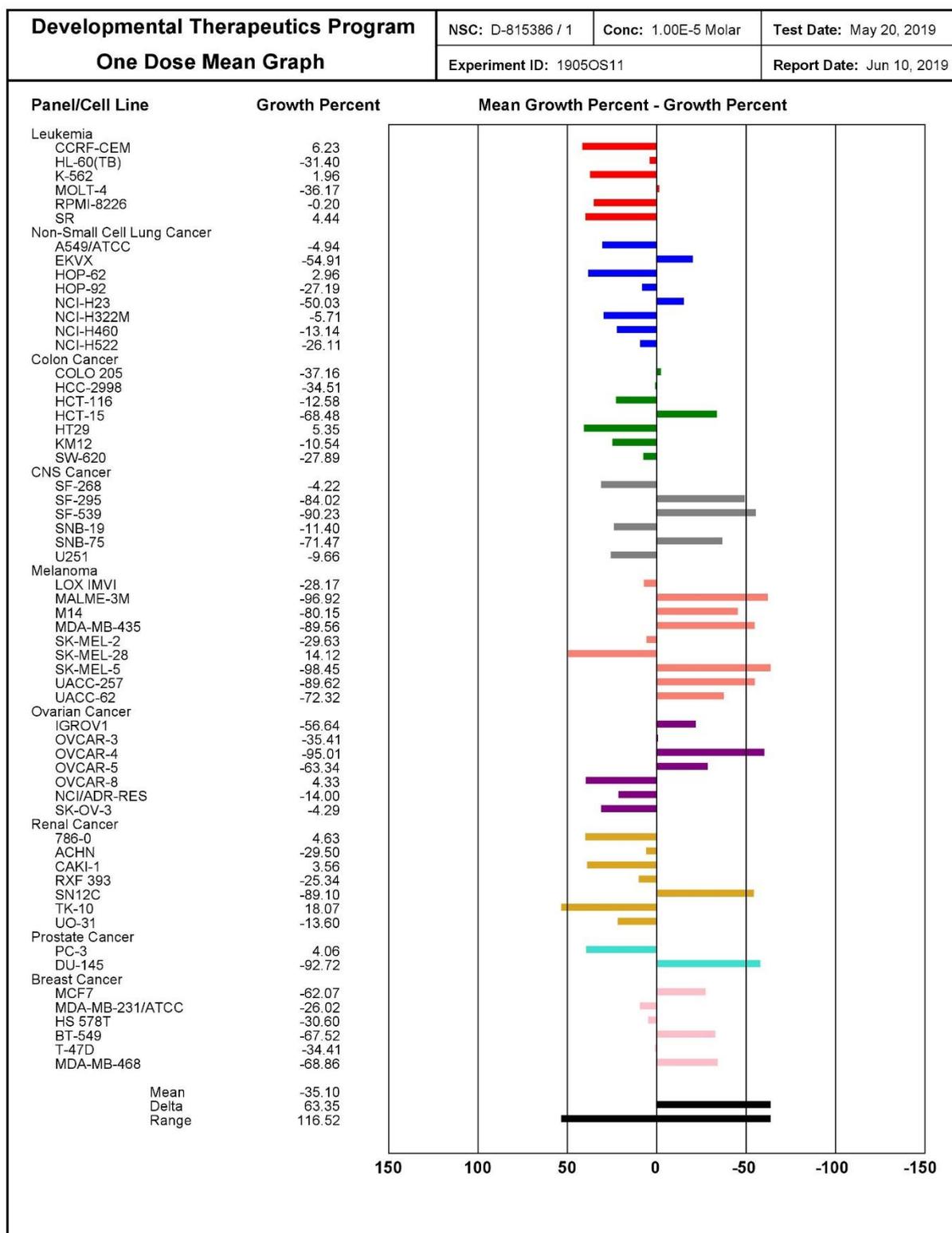
Compound 14



Compound 15

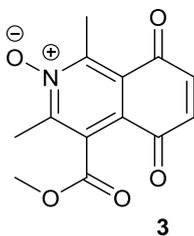
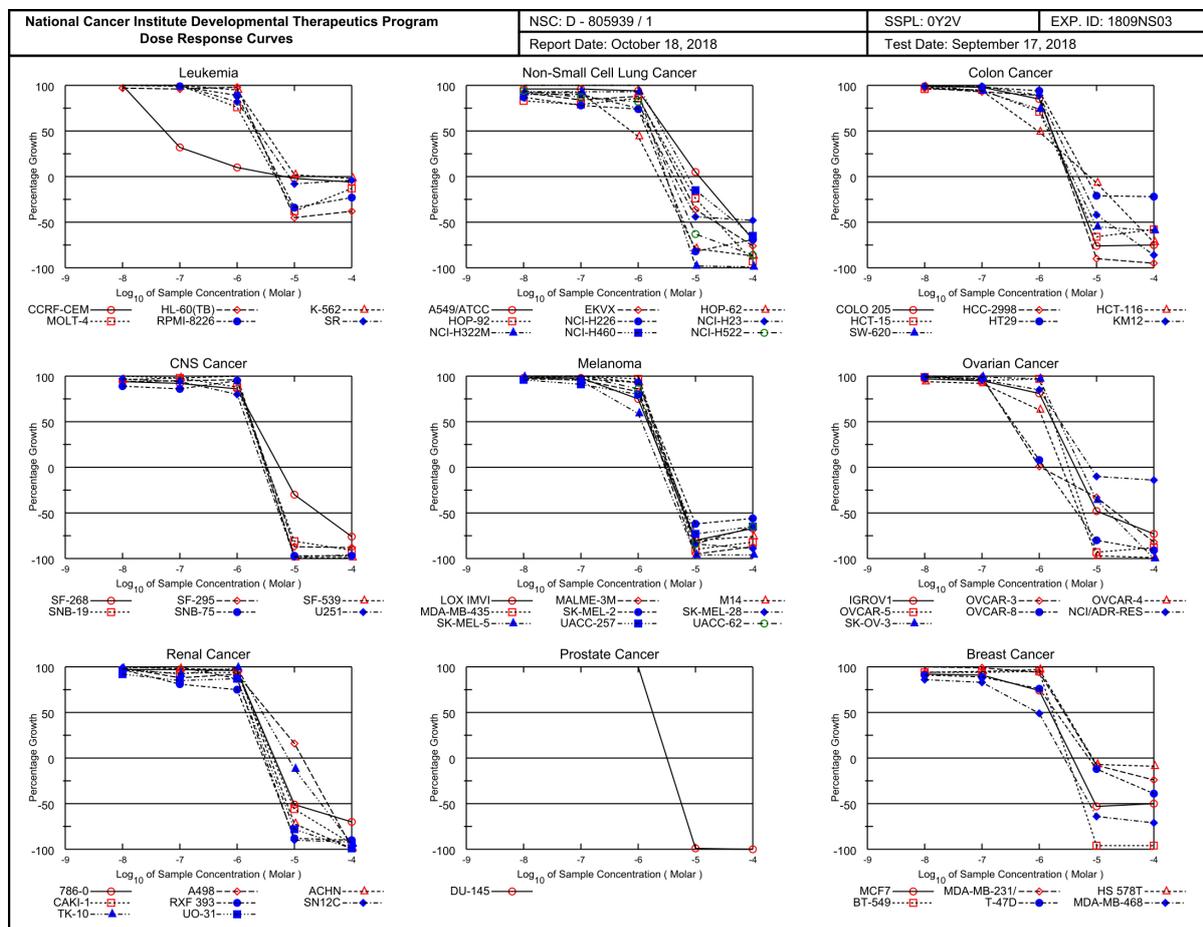


Compound 16



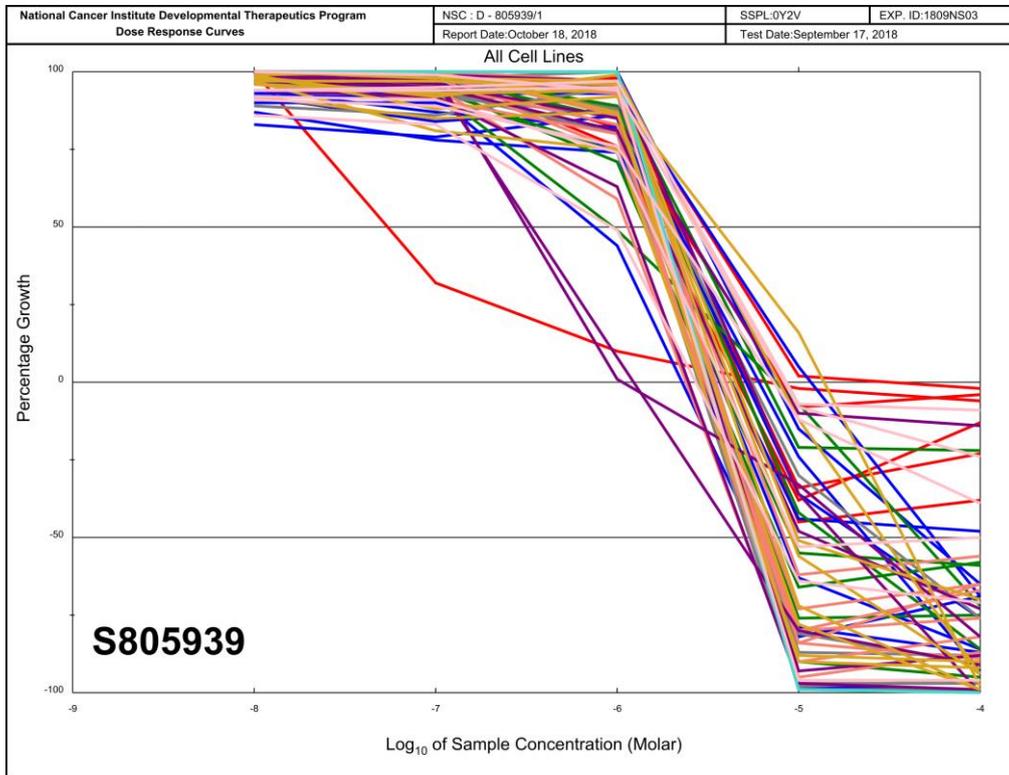
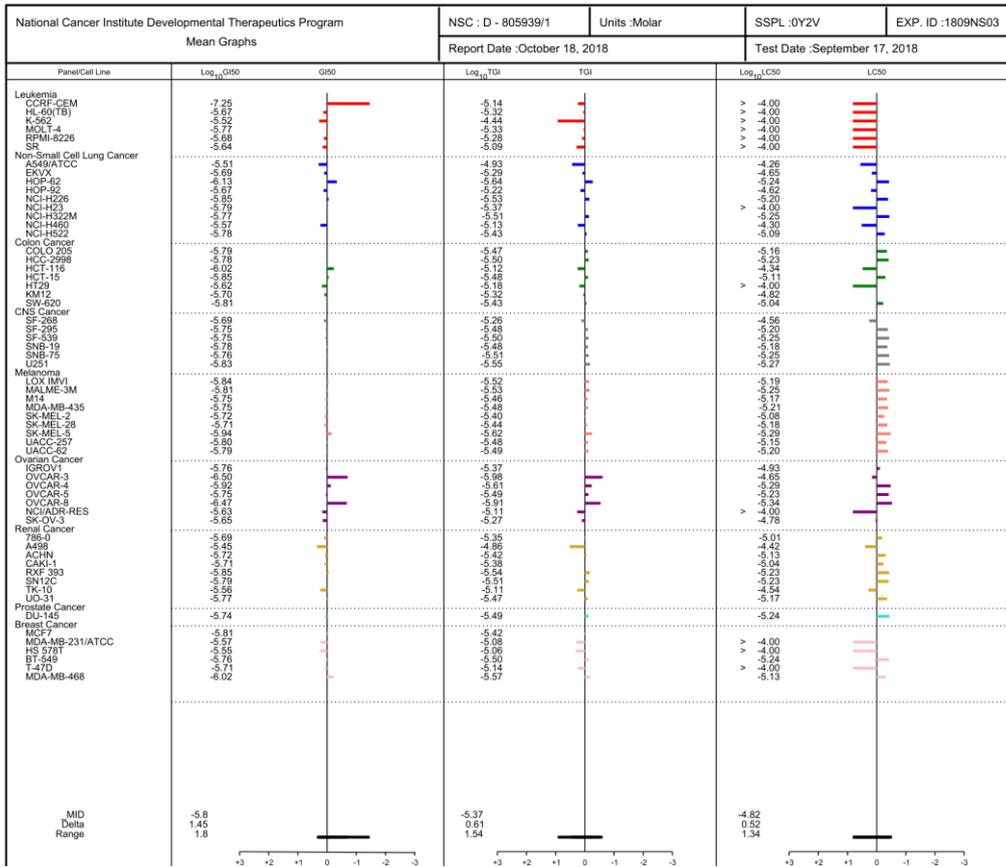
NCI60 – Five Dose Data

Compound 3



**National Cancer Institute Developmental Therapeutics Program
In-Vitro Testing Results**

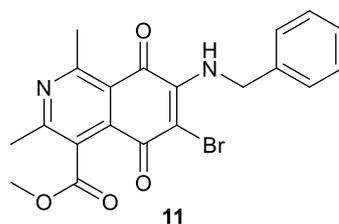
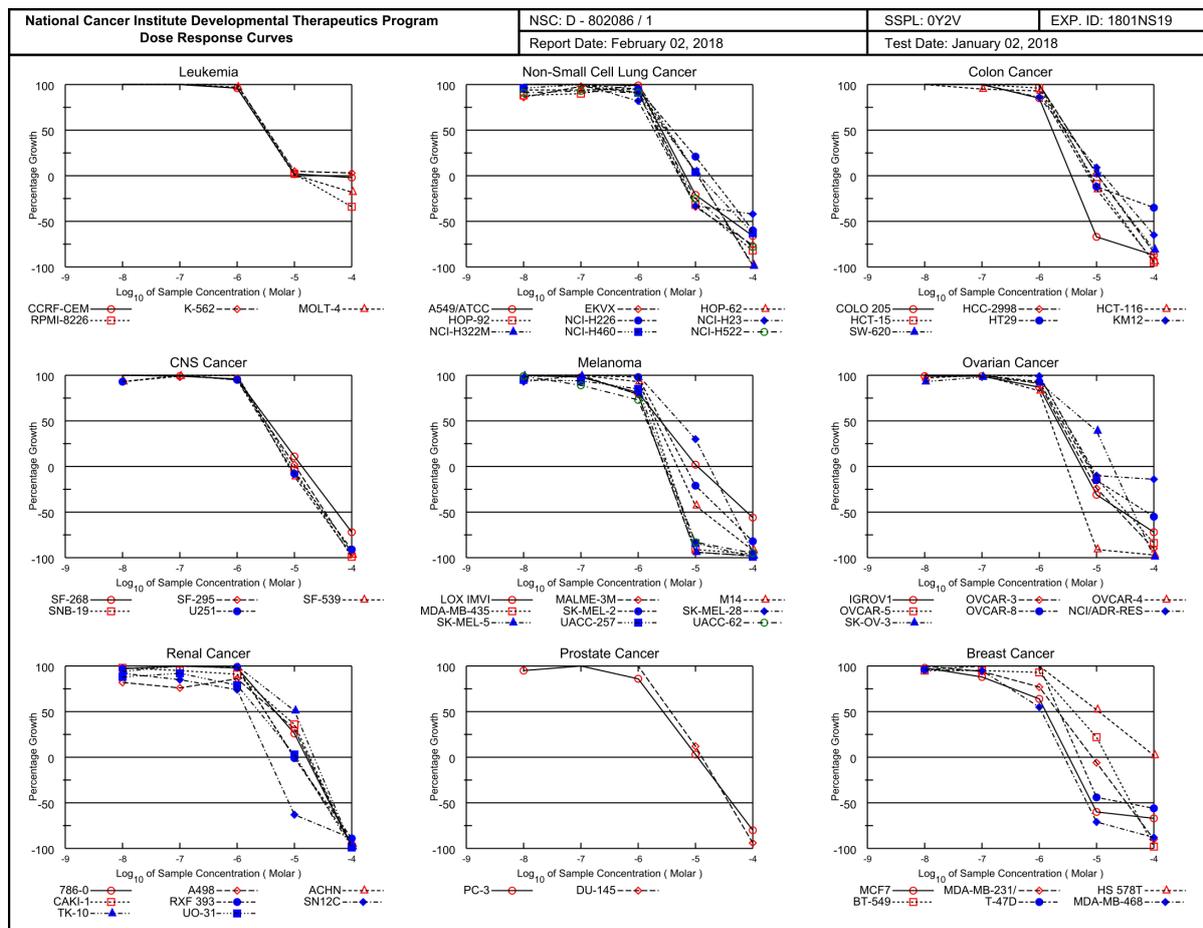
NSC : D - 805939 / 1		Experiment ID : 1809NS03					Test Type : 08		Units : Molar						
Report Date : October 18, 2018		Test Date : September 17, 2018					QNS :		MC :						
COMI : RK CH 0.0.2		Stain Reagent : SRB Dual-Pass Related					SSPL : 0Y2V								
Panel/Cell Line	Time Zero	Log10 Concentration										GI50	TGI	LC50	
		Ctrl	-8.0	-7.0	-6.0	-5.0	-4.0	-8.0	-7.0	-6.0	-5.0				-4.0
Leukemia															
CCRF-CEM	0.555	2.485	2.576	1.164	0.753	0.546	0.521	105	32	10	-2	-6	5.59E-8	7.30E-6	> 1.00E-4
HL-60(TB)	0.925	3.282	3.219	3.192	3.233	0.508	0.577	97	96	98	-45	-38	2.16E-6	4.84E-6	> 1.00E-4
K-562	0.278	2.640	2.781	2.715	2.516	0.326	0.274	106	103	95	2	-2	3.04E-6	3.60E-5	> 1.00E-4
MOLT-4	0.645	2.975	3.012	2.966	2.415	0.401	0.561	102	100	76	-38	-13	1.69E-6	4.65E-6	> 1.00E-4
RPMI-8226	0.838	2.851	2.887	2.838	2.622	0.554	0.644	102	99	89	-34	-23	2.07E-6	5.29E-6	> 1.00E-4
SR	0.345	1.836	1.871	1.878	1.571	0.318	0.330	102	103	82	-8	-4	2.28E-6	8.19E-6	> 1.00E-4
Non-Small Cell Lung Cancer															
A549/ATCC	0.431	2.311	2.240	2.229	2.199	0.523	0.134	96	96	94	5	-69	3.12E-6	1.16E-5	5.53E-5
EKVX	0.872	2.152	2.054	1.953	1.999	0.558	0.207	92	84	88	-36	-76	2.02E-6	5.12E-6	2.22E-5
HOP-62	0.326	1.375	1.291	1.296	0.785	0.068	0.043	92	92	44	-79	-87	7.44E-7	2.27E-6	5.79E-6
HOP-92	0.922	1.477	1.383	1.360	1.400	0.699	0.069	83	79	86	-24	-93	2.12E-6	6.03E-6	2.38E-5
NCI-H226	1.257	2.301	2.163	2.069	2.026	0.232	0.385	87	78	74	-82	-69	1.42E-6	2.98E-6	6.26E-6
NCI-H23	0.664	2.229	2.066	2.074	1.843	0.371	0.345	90	90	75	-44	-48	1.63E-6	4.27E-6	> 1.00E-4
NCI-H322M	0.681	2.241	2.137	2.137	2.136	0.015	0.005	93	93	93	-98	-99	1.68E-6	3.08E-6	5.62E-6
NCI-H460	0.353	3.149	3.196	3.184	3.149	0.300	0.123	102	101	100	-15	-65	2.72E-6	7.40E-6	4.99E-5
NCI-H522	0.827	2.555	2.456	2.334	2.247	0.304	0.117	94	87	82	-63	-86	1.66E-6	3.67E-6	8.11E-6
Colon Cancer															
COLO 205	0.375	2.012	1.989	1.976	1.759	0.089	0.095	99	98	85	-76	-75	1.64E-6	3.35E-6	6.85E-6
HCC-2998	1.137	3.308	3.252	3.161	3.062	0.109	0.056	97	93	89	-90	-95	1.64E-6	3.13E-6	5.95E-6
HCT-116	0.201	2.397	2.353	2.262	1.275	0.187	0.057	98	94	49	-7	-72	9.45E-7	7.50E-6	4.60E-5
HCT-15	0.362	2.375	2.285	2.266	1.793	0.125	0.151	96	95	71	-66	-58	1.43E-6	3.31E-6	7.69E-6
HT29	0.256	1.988	2.047	1.951	1.884	0.202	0.200	103	98	94	-21	-22	2.41E-6	6.54E-6	> 1.00E-4
KM12	0.576	2.845	2.820	2.818	2.602	0.333	0.084	99	99	89	-42	-86	1.99E-6	4.77E-6	1.51E-5
SW-620	0.290	1.997	2.057	1.901	1.557	0.130	0.119	104	94	74	-55	-59	1.54E-6	3.74E-6	9.09E-6
CNS Cancer															
SF-268	0.781	2.278	2.195	2.153	2.070	0.548	0.191	94	92	86	-30	-76	2.05E-6	5.52E-6	2.76E-5
SF-295	1.102	3.203	3.083	3.096	3.110	0.146	0.132	94	95	96	-87	-88	1.78E-6	3.34E-6	6.28E-6
SF-539	1.016	2.836	2.769	2.792	2.855	0.008	0.011	96	98	101	-99	-99	1.80E-6	3.20E-6	5.68E-6
SNB-19	0.588	2.250	2.244	2.215	2.048	0.112	0.055	100	98	88	-81	-91	1.68E-6	3.31E-6	6.55E-6
SNB-75	0.854	1.672	1.581	1.555	1.634	0.022	0.028	89	86	95	-97	-97	1.72E-6	3.12E-6	5.67E-6
U251	0.520	2.449	2.390	2.336	2.070	0.013	0.022	97	94	80	-98	-96	1.48E-6	2.83E-6	5.40E-6
Melanoma															
LOX IMVI	0.758	3.337	3.279	3.275	2.681	0.154	0.251	98	98	75	-80	-67	1.44E-6	3.04E-6	6.42E-6
MALME-3M	0.842	1.822	1.797	1.786	1.658	0.040	0.114	97	96	83	-95	-87	1.53E-6	2.92E-6	5.57E-6
M14	0.458	2.172	2.140	2.179	2.058	0.090	0.110	98	100	93	-80	-76	1.78E-6	3.45E-6	6.69E-6
MDA-MB-435	0.666	2.990	2.981	3.016	2.920	0.069	0.119	100	101	97	-90	-82	1.79E-6	3.31E-6	6.13E-6
SK-MEL-2	1.247	2.886	2.888	2.832	2.770	0.479	0.553	100	97	93	-62	-56	1.89E-6	3.99E-6	8.41E-6
SK-MEL-28	0.839	2.540	2.611	2.609	2.630	0.135	0.095	104	104	105	-84	-89	1.96E-6	3.60E-6	6.62E-6
SK-MEL-5	1.028	3.204	3.187	3.095	2.313	0.046	0.037	99	95	59	-96	-96	1.14E-6	2.41E-6	5.07E-6
UACC-257	0.764	2.132	2.082	2.009	1.856	0.210	0.270	96	91	80	-73	-65	1.57E-6	3.34E-6	7.11E-6
UACC-62	0.978	2.861	2.961	2.913	2.602	0.155	0.344	105	103	86	-84	-65	1.63E-6	3.21E-6	6.30E-6
Ovarian Cancer															
IGROV1	0.412	1.984	1.937	1.900	1.690	0.214	0.112	97	95	81	-48	-73	1.74E-6	4.24E-6	1.18E-5
OVCAR-3	0.511	1.863	1.895	1.846	0.521	0.341	0.094	102	99	1	-33	-82	3.14E-7	1.05E-6	2.22E-5
OVCAR-4	0.631	1.631	1.572	1.550	1.257	0.019	0.009	94	92	63	-97	-99	1.20E-6	2.47E-6	5.08E-6
OVCAR-5	0.576	1.648	1.636	1.594	1.615	0.038	0.069	99	95	97	-93	-88	1.76E-6	3.23E-6	5.91E-6
OVCAR-8	0.342	1.768	1.757	1.730	0.458	0.068	0.030	99	97	8	-80	-91	3.39E-7	1.24E-6	4.54E-6
NCI/ADR-RES	0.682	2.396	2.392	2.321	2.142	0.611	0.586	100	96	85	-10	-14	2.33E-6	7.78E-6	> 1.00E-4
SK-OV-3	0.558	1.690	1.694	1.681	1.656	0.359	0.002	100	99	97	-36	-100	2.26E-6	5.38E-6	1.67E-5
Renal Cancer															
786-0	0.670	2.699	2.631	2.641	2.627	0.328	0.201	97	97	96	-51	-70	2.07E-6	4.51E-6	9.84E-6
A498	1.579	2.461	2.454	2.354	2.388	1.724	0.034	99	88	92	16	-98	3.58E-6	1.39E-5	3.81E-5
ACHN	0.355	1.655	1.670	1.634	1.619	0.101	0.003	101	98	97	-72	-99	1.90E-6	3.77E-6	7.45E-6
CAKI-1	0.878	2.444	2.376	2.337	2.344	0.382	0.051	96	93	94	-56	-94	1.95E-6	4.20E-6	9.05E-6
RXF 393	1.198	1.965	1.945	1.816	1.772	0.143	0.115	97	81	75	-88	-90	1.42E-6	2.88E-6	5.84E-6
SN12C	0.754	2.932	2.901	2.970	2.657	0.074	0.062	99	102	87	-90	-92	1.62E-6	3.10E-6	5.93E-6
TK-10	0.792	2.121	2.089	2.013	2.104	0.694	0.050	98	92	99	-12	-94	2.74E-6	7.74E-6	2.90E-5
UO-31	0.771	2.208	2.097	1.989	2.029	0.172	0.006	92	85	87	-78	-99	1.69E-6	3.39E-6	6.80E-6
Prostate Cancer															
DU-145	0.477	1.878	1.929	1.941	1.912	0.003	0.001	104	105	102	-99	-100	1.82E-6	3.22E-6	5.69E-6
Breast Cancer															
MCF7	0.631	3.142	2.937	2.922	2.493	0.295	0.317	92	91	74	-53	-50	1.55E-6	3.82E-6	.
MDA-MB-231/ATCC	0.725	1.663	1.711	1.653	1.604	0.665	0.549	105	99	94	-8	-24	2.68E-6	8.28E-6	> 1.00E-4
HS 578T	1.104	2.260	2.190	2.199	2.225	1.032	1.009	94	95	97	-7	-9	2.84E-6	8.64E-6	> 1.00E-4
BT-549	1.199	2.726	2.638	2.636	2.650	0.045	0.046	94	94	95	-96	-96	1.72E-6	3.14E-6	5.73E-6
T-47D	0.489	1.196	1.132	1.116	1.026	0.429	0.299	91	89	76	-12	-39	1.97E-6	7.26E-6	> 1.00E-4
MDA-MB-468	0.945	1.631	1.539	1.517	1.283	0.337	0.276	86	83	49	-64	-71	9.46E-7	2.71E-6	7.48E-6



Mean of effective endpoints across 59 cell lines for compound 3 as Log₁₀ Concentration (SD)

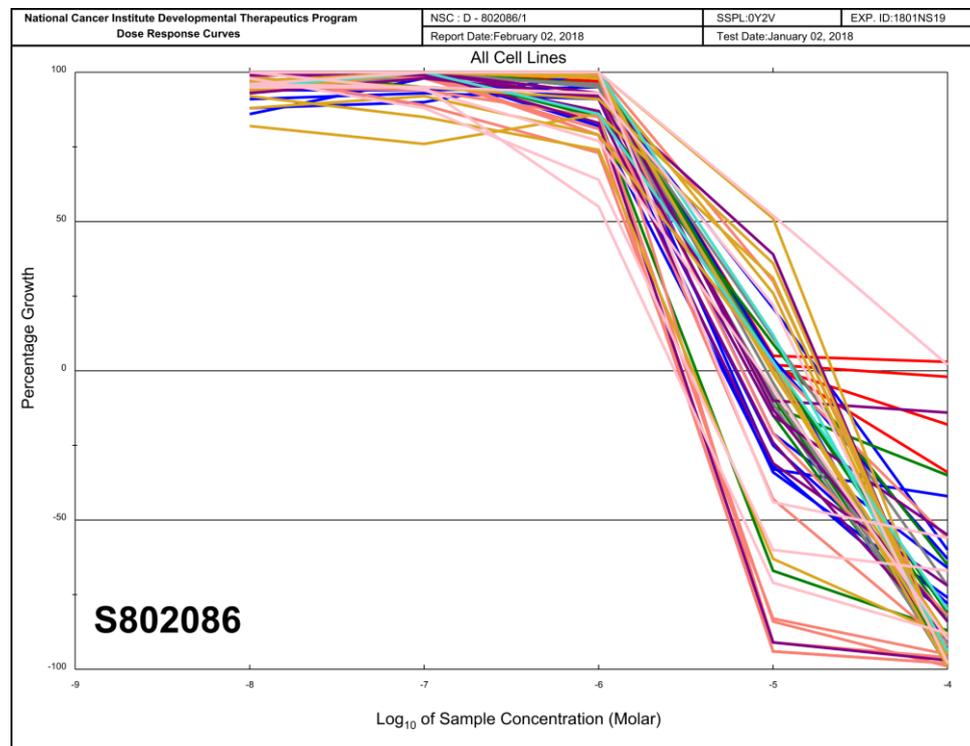
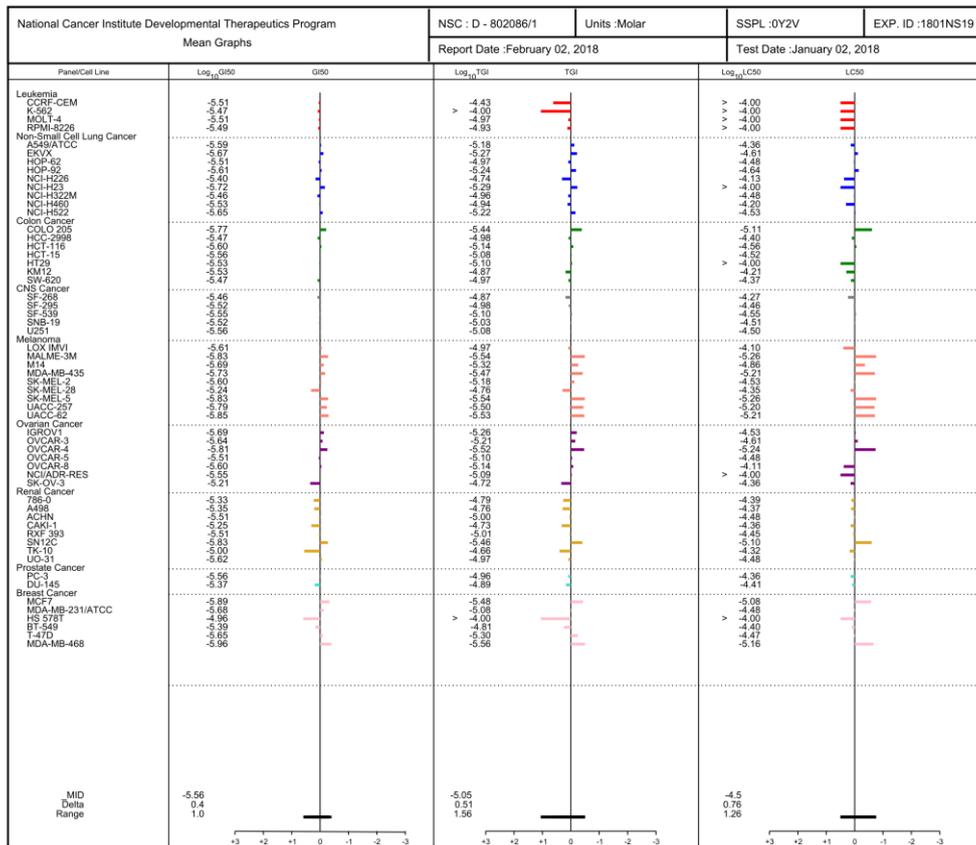
GI₅₀ -5.8 (±0.26); TGI -5.37 (±0.24); LC₅₀ -4.82 (±0.41)

Compound 11



**National Cancer Institute Developmental Therapeutics Program
In-Vitro Testing Results**

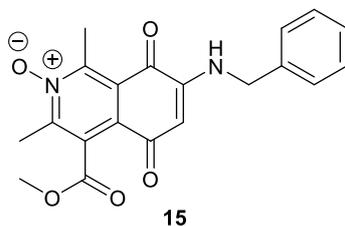
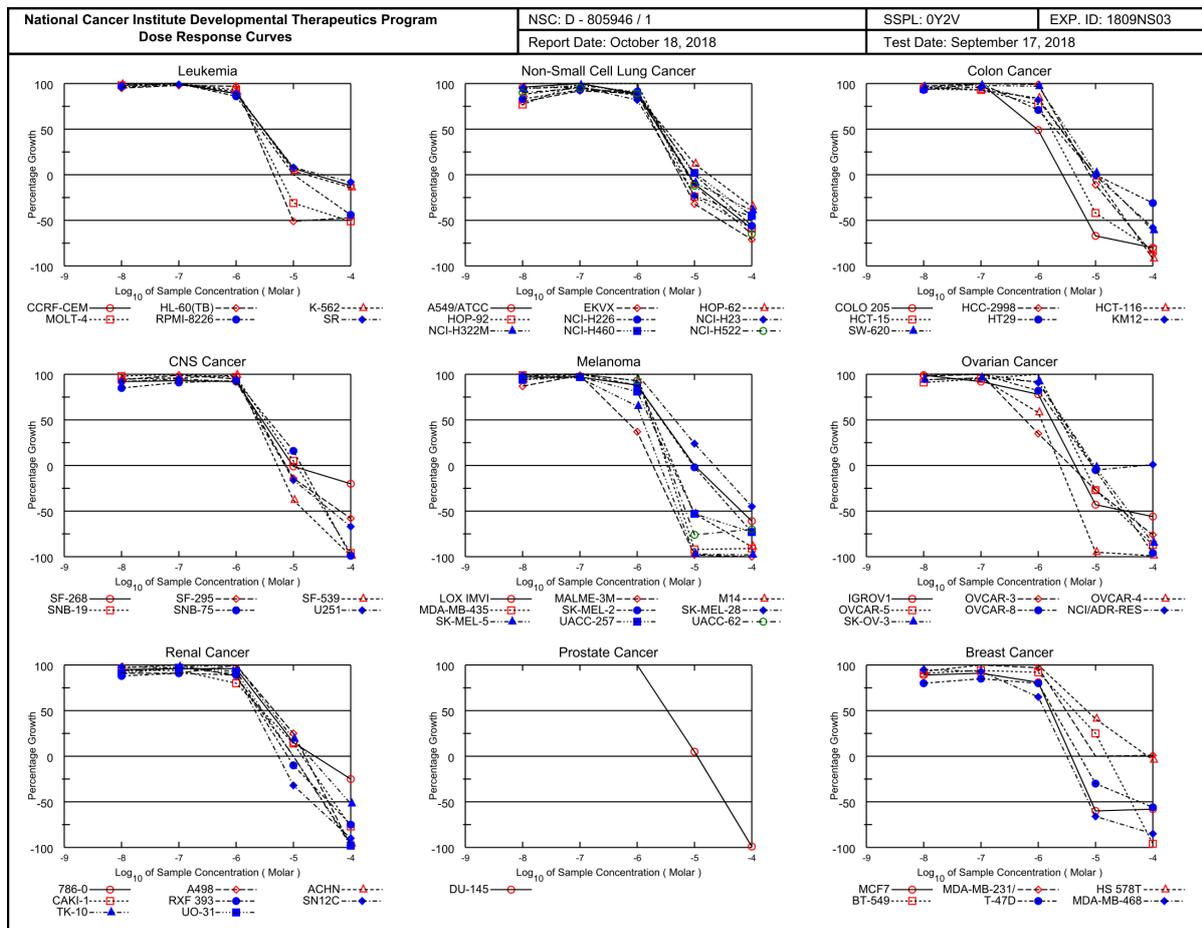
NSC : D - 802086 / 1		Experiment ID : 1801NS19					Test Type : 08		Units : Molar						
Report Date : February 02, 2018		Test Date : January 02, 2018					QNS :		MC :						
COMI : AGS 1.1.7.1		Stain Reagent : SRB Dual-Pass Related					SSPL : 0Y2V								
Panel/Cell Line	Time Zero	Log10 Concentration										GI50	TGI	LC50	
		Ctrl	-8.0	-7.0	-6.0	-5.0	-4.0	-8.0	-7.0	-6.0	-5.0				-4.0
Leukemia															
CCRF-CEM	0.289	1.705	1.732	1.758	1.654	0.321	0.284	102	104	96	2	-2	3.11E-6	3.68E-5	> 1.00E-4
K-562	0.074	0.882	0.919	0.907	0.880	0.116	0.102	104	103	100	5	3	3.36E-6	> 1.00E-4	> 1.00E-4
MOLT-4	0.476	2.189	2.264	2.254	2.144	0.487	0.391	104	104	97	1	-18	3.09E-6	1.08E-5	> 1.00E-4
RPMI-8226	0.592	2.130	2.134	2.224	2.125	0.630	0.392	100	106	100	2	-34	3.24E-6	1.17E-5	> 1.00E-4
Non-Small Cell Lung Cancer															
A549/ATCC	0.319	1.621	1.616	1.626	1.612	0.251	0.108	100	100	99	-21	-66	2.56E-6	6.64E-6	4.35E-5
EKVX	0.408	1.173	1.063	1.157	1.101	0.270	0.100	86	98	91	-34	-76	2.12E-6	5.35E-6	2.44E-5
HOP-62	0.856	1.965	1.896	1.901	1.914	0.895	0.013	94	94	95	4	-98	3.12E-6	1.08E-5	3.35E-5
HOP-92	1.068	1.524	1.471	1.479	1.537	0.726	0.188	88	90	103	-32	-82	2.46E-6	5.78E-6	2.27E-5
NCI-H226	0.617	1.238	1.254	1.244	1.205	0.745	0.246	103	101	95	21	-60	4.01E-6	1.80E-5	7.49E-5
NCI-H23	0.479	1.855	1.883	1.916	1.603	0.323	0.280	102	104	82	-33	-42	1.89E-6	5.19E-6	> 1.00E-4
NCI-H322M	0.544	1.409	1.452	1.468	1.444	0.576	0.006	105	107	104	4	-99	3.45E-6	1.09E-5	3.34E-5
NCI-H460	0.160	1.514	1.465	1.658	1.387	0.214	0.059	96	111	91	4	-63	2.94E-6	1.15E-5	6.37E-5
NCI-H522	0.913	2.105	1.995	2.017	1.996	0.685	0.204	91	93	91	-25	-78	2.25E-6	6.09E-6	2.98E-5
Colon Cancer															
COLO 205	0.426	1.092	1.122	1.108	0.994	0.141	0.054	104	102	85	-67	-87	1.70E-6	3.63E-6	7.73E-6
HCC-2998	0.576	2.115	2.133	2.136	2.182	0.607	0.091	101	101	104	2	-84	3.40E-6	1.05E-5	4.00E-5
HCT-116	0.234	1.855	1.873	1.772	1.747	0.198	0.014	101	95	93	-15	-94	2.50E-6	7.22E-6	2.75E-5
HCT-15	0.247	1.404	1.403	1.463	1.362	0.226	0.013	100	105	96	-9	-95	2.76E-6	8.26E-6	3.01E-5
HT29	0.221	1.239	1.326	1.315	1.291	0.196	0.143	109	107	105	-12	-35	2.97E-6	7.96E-6	> 1.00E-4
KM12	0.408	1.831	1.963	1.936	1.626	0.543	0.141	109	107	86	9	-65	2.93E-6	1.34E-5	6.22E-5
SW-620	0.273	1.897	2.004	1.968	1.959	0.312	0.053	107	104	104	2	-81	3.39E-6	1.07E-5	4.28E-5
CNS Cancer															
SF-268	0.510	1.729	1.731	1.715	1.677	0.643	0.142	100	99	96	11	-72	3.46E-6	1.35E-5	5.41E-5
SF-295	0.542	2.092	2.140	2.201	2.020	0.566	0.029	103	107	95	2	-95	3.04E-6	1.04E-5	3.43E-5
SF-539	0.664	2.045	1.951	2.031	2.053	0.593	0.017	93	99	101	-11	-97	2.85E-6	8.02E-6	2.84E-5
SNB-19	0.431	1.469	1.526	1.502	1.469	0.416	0.004	105	103	100	-4	-99	3.04E-6	9.23E-6	3.06E-5
U251	0.289	1.344	1.269	1.352	1.294	0.266	0.025	93	101	95	-8	-91	2.74E-6	8.34E-6	3.19E-5
Melanoma															
LOX IMVI	0.315	2.204	2.211	2.166	1.839	0.352	0.139	100	98	81	2	-56	2.45E-6	1.08E-5	7.91E-5
MALME-3M	0.432	0.902	0.922	0.938	0.802	0.025	0.008	104	108	79	-94	-98	1.47E-6	2.85E-6	5.55E-6
M14	0.362	1.264	1.268	1.298	1.197	0.206	0.029	100	104	93	-43	-92	2.06E-6	4.81E-6	1.38E-5
MDA-MB-435	0.513	2.161	2.162	2.229	2.190	0.048	0.019	100	104	102	-91	-96	1.86E-6	3.38E-6	6.15E-6
SK-MEL-2	1.130	2.075	2.088	2.086	2.054	0.890	0.199	101	101	98	-21	-82	2.52E-6	6.63E-6	2.95E-5
SK-MEL-28	0.633	1.768	1.694	1.921	1.931	0.973	0.039	93	113	114	30	-94	5.79E-6	1.74E-5	4.42E-5
SK-MEL-5	0.716	2.965	2.952	2.940	2.488	0.041	0.014	99	99	79	-94	-98	1.47E-6	2.85E-6	5.54E-6
UACC-257	1.049	2.162	2.101	2.092	1.998	0.168	0.009	95	94	85	-84	-99	1.62E-6	3.19E-6	6.30E-6
UACC-62	1.056	2.718	2.696	2.540	2.271	0.176	0.048	99	89	73	-83	-95	1.41E-6	2.93E-6	6.12E-6
Ovarian Cancer															
IGROV1	0.426	1.584	1.567	1.574	1.428	0.294	0.120	99	99	87	-31	-72	2.05E-6	5.45E-6	2.92E-5
OVCAR-3	0.434	1.580	1.718	1.701	1.478	0.329	0.044	112	110	91	-24	-90	2.27E-6	6.16E-6	2.46E-5
OVCAR-4	0.753	1.696	1.663	1.728	1.536	0.066	0.021	97	103	83	-91	-97	1.55E-6	2.99E-6	5.80E-6
OVCAR-5	0.588	1.394	1.411	1.422	1.480	0.514	0.094	102	104	111	-13	-84	3.11E-6	7.91E-6	3.34E-5
OVCAR-8	0.444	1.735	1.765	1.739	1.650	0.377	0.202	102	100	93	-15	-55	2.51E-6	7.24E-6	7.68E-5
NCI/ADR-RES	0.407	1.409	1.416	1.443	1.400	0.368	0.350	101	103	99	-10	-14	2.83E-6	8.16E-6	> 1.00E-4
SK-OV-3	0.819	1.515	1.467	1.504	1.459	1.091	0.008	93	98	92	39	-99	6.20E-6	1.92E-5	4.41E-5
Renal Cancer															
786-0	0.554	2.000	1.951	2.014	1.970	0.932	0.012	97	101	98	26	-98	4.65E-6	1.63E-5	4.11E-5
A498	1.381	2.098	1.971	1.927	2.000	1.600	0.024	82	76	86	31	-98	4.48E-6	1.73E-5	4.22E-5
ACHN	0.419	1.401	1.531	1.506	1.380	0.419	0.020	113	111	98	.	-95	3.08E-6	9.97E-6	3.35E-5
CAKI-1	0.532	1.741	1.714	1.681	1.636	0.973	0.011	98	95	91	36	-98	5.66E-6	1.87E-5	4.40E-5
RXF 393	1.040	1.684	1.663	1.756	1.677	1.026	0.110	97	111	99	-1	-89	3.08E-6	9.69E-6	3.57E-5
SN12C	0.569	1.838	1.738	1.654	1.502	0.209	0.060	92	85	74	-63	-89	1.49E-6	3.45E-6	8.00E-6
TK-10	0.742	1.485	1.440	1.510	1.687	1.118	0.019	94	103	127	51	-98	1.01E-5	2.19E-5	4.78E-5
UO-31	0.737	2.138	1.969	2.021	1.844	0.781	0.004	88	92	79	3	-99	2.41E-6	1.07E-5	3.30E-5
Prostate Cancer															
PC-3	0.442	1.815	1.748	1.819	1.624	0.487	0.089	95	100	86	3	-80	2.73E-6	1.09E-5	4.37E-5
DU-145	0.292	1.087	1.159	1.322	1.202	0.388	0.018	109	130	114	12	-94	4.26E-6	1.30E-5	3.85E-5
Breast Cancer															
MCF7	0.278	1.615	1.585	1.458	1.136	0.112	0.093	98	88	64	-60	-67	1.30E-6	3.29E-6	8.32E-6
MDA-MB-231/ATCC	0.485	1.227	1.235	1.181	1.056	0.455	0.049	101	94	77	-6	-90	2.11E-6	8.40E-6	3.33E-5
HS 578T	1.070	2.082	2.137	2.116	2.150	1.594	1.093	105	103	107	52	2	1.08E-5	> 1.00E-4	> 1.00E-4
BT-549	1.061	2.154	2.103	2.096	2.080	1.307	0.025	95	95	93	22	-98	4.08E-6	1.54E-5	4.01E-5
T-47D	0.737	1.337	1.315	1.361	1.346	0.416	0.327	96	104	101	-44	-56	2.26E-6	5.00E-6	3.37E-5
MDA-MB-468	0.726	1.339	1.318	1.309	1.066	0.214	0.086	96	95	55	-71	-88	1.10E-6	2.75E-6	6.87E-6



Mean of effective endpoints across 57 cell lines for compound 11 as Log₁₀ Concentration (SD)

GI₅₀ -5.56 (±0.19); TGI -5.05 (±0.32); LC₅₀ -4.5 (±0.36)

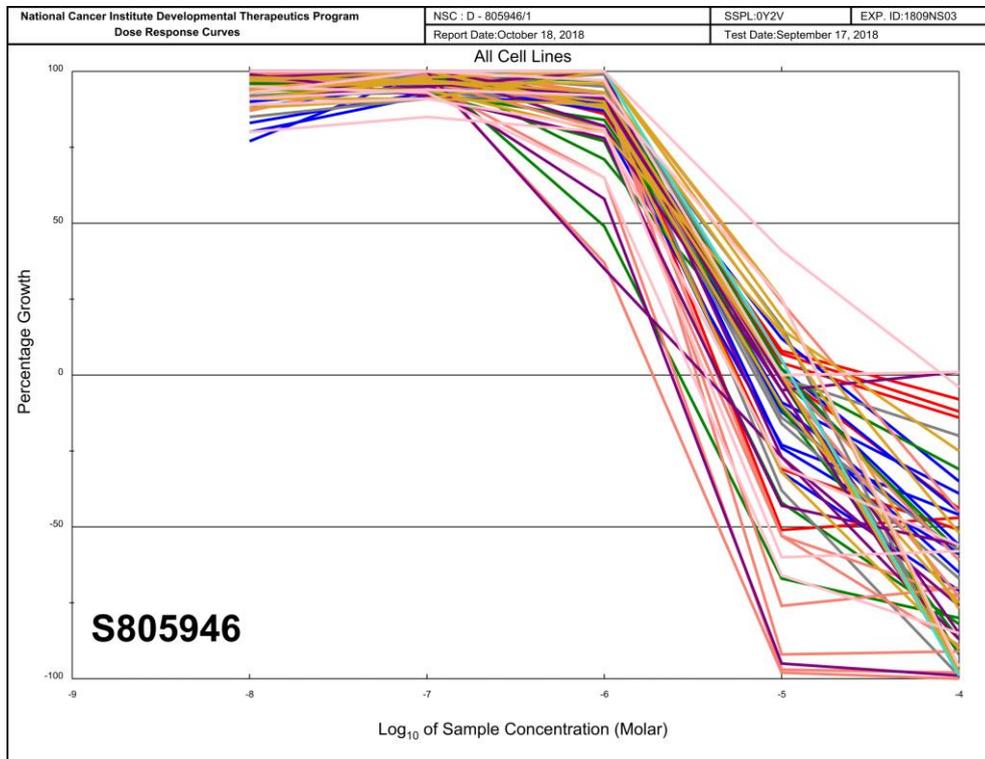
Compound 15



**National Cancer Institute Developmental Therapeutics Program
In-Vitro Testing Results**

NSC : D - 805946 / 1		Experiment ID : 1809NS03					Test Type : 08					Units : Molar			
Report Date : October 18, 2018		Test Date : September 17, 2018					QNS :					MC :			
COMI : RK LEI 1-007		Stain Reagent : SRB Dual-Pass Related					SSPL : 0Y2V								
Panel/Cell Line	Time Zero	Log10 Concentration										GI50	TGI	LC50	
		Ctrl	-8.0	-7.0	-6.0	-5.0	-4.0	-8.0	-7.0	-6.0	-5.0				-4.0
Leukemia															
CCRF-CEM	0.555	2.485	2.507	2.558	2.277	0.683	0.487	101	104	89	7	-12	2.98E-6	2.23E-5	> 1.00E-4
HL-60(TB)	0.925	3.282	3.170	3.242	3.216	0.455	0.493	95	98	97	-51	-47	2.08E-6	4.54E-6	.
K-562	0.278	2.640	2.623	2.709	2.421	0.367	0.239	99	103	91	4	-14	2.94E-6	1.63E-5	> 1.00E-4
MOLT-4	0.645	2.975	2.932	3.041	2.803	0.444	0.317	98	103	93	-31	-51	2.21E-6	5.60E-6	9.05E-5
RPMI-8226	0.838	2.851	2.782	2.866	2.561	0.843	0.469	97	101	86	.	-44	2.61E-6	1.01E-5	> 1.00E-4
SR	0.345	1.836	1.772	1.822	1.667	0.461	0.318	96	99	89	8	-8	3.00E-6	3.14E-5	> 1.00E-4
Non-Small Cell Lung Cancer															
A549/ATCC	0.431	2.311	2.236	2.318	2.101	0.389	0.178	96	100	89	-10	-59	2.47E-6	7.94E-6	6.61E-5
EKVX	0.872	2.152	1.902	2.044	2.011	0.590	0.254	80	92	89	-32	-71	2.09E-6	5.41E-6	2.87E-5
HOP-62	0.326	1.375	1.249	1.336	1.236	0.452	0.211	88	96	87	12	-35	3.10E-6	1.79E-5	> 1.00E-4
HOP-92	0.922	1.477	1.349	1.486	1.533	0.699	0.383	77	102	110	-24	-59	2.80E-6	6.61E-6	5.65E-5
NCI-H226	1.257	2.301	2.119	2.226	2.207	1.252	0.552	83	93	91	.	-56	2.81E-6	9.90E-6	7.78E-5
NCI-H23	0.664	2.229	2.157	2.169	1.952	0.514	0.357	95	96	82	-23	-46	2.03E-6	6.09E-6	> 1.00E-4
NCI-H322M	0.681	2.241	2.153	2.206	2.106	0.621	0.414	94	98	91	-9	-39	2.59E-6	8.15E-6	> 1.00E-4
NCI-H460	0.353	3.149	3.156	3.200	2.805	0.400	0.195	100	102	88	2	-45	2.74E-6	1.09E-5	> 1.00E-4
NCI-H522	0.827	2.555	2.380	2.474	2.371	0.728	0.294	90	95	89	-12	-65	2.45E-6	7.62E-6	5.29E-5
Colon Cancer															
COLO 205	0.375	2.012	2.005	2.025	1.185	0.125	0.075	100	101	49	-67	-80	9.77E-7	2.67E-6	7.19E-6
HCC-2998	1.137	3.308	3.244	3.312	3.290	1.015	0.151	97	100	99	-11	-87	2.80E-6	7.98E-6	3.28E-5
HCT-116	0.201	2.397	2.310	2.249	2.038	0.197	0.017	96	93	84	-2	-92	2.47E-6	9.48E-6	3.42E-5
HCT-15	0.362	2.375	2.261	2.238	1.921	0.210	0.065	94	93	77	-42	-82	1.70E-6	4.44E-6	1.57E-5
HT29	0.256	1.988	1.866	2.083	1.482	0.261	0.178	93	106	71	.	-31	1.97E-6	1.02E-5	> 1.00E-4
KM12	0.576	2.845	2.708	2.759	2.430	0.568	0.244	94	96	82	-1	-58	2.40E-6	9.60E-6	7.31E-5
SW-620	0.290	1.997	1.937	1.958	1.953	0.317	0.114	96	98	97	2	-61	3.12E-6	1.06E-5	6.70E-5
CNS Cancer															
SF-268	0.781	2.278	2.165	2.180	2.154	0.771	0.624	92	93	92	-1	-20	2.81E-6	9.69E-6	> 1.00E-4
SF-295	1.102	3.203	3.080	3.181	3.099	0.952	0.468	94	99	95	-14	-58	2.60E-6	7.49E-6	6.74E-5
SF-539	1.016	2.836	2.742	2.767	2.823	0.632	0.006	95	96	99	-38	-99	2.29E-6	5.30E-6	1.58E-5
SNB-19	0.588	2.250	2.217	2.360	2.200	0.673	0.025	98	107	97	5	-96	3.25E-6	1.12E-5	3.52E-5
SNB-75	0.854	1.672	1.552	1.603	1.612	0.988	0.013	85	91	93	16	-99	3.62E-6	1.39E-5	3.78E-5
U251	0.520	2.449	2.288	2.354	2.302	0.437	0.170	92	95	92	-16	-67	2.46E-6	7.11E-6	4.60E-5
Melanoma															
LOX IMVI	0.758	3.337	3.255	3.272	3.031	0.770	0.296	97	97	88	.	-61	2.72E-6	1.02E-5	6.62E-5
MALME-3M	0.842	1.822	1.692	1.815	1.204	0.020	.	87	99	37	-98	-100	6.17E-7	1.88E-6	4.43E-6
M14	0.458	2.172	2.061	2.167	2.051	0.217	0.049	94	100	93	-53	-89	1.97E-6	4.35E-6	9.58E-6
MDA-MB-435	0.666	2.990	2.966	3.062	2.982	0.050	0.058	99	103	100	-92	-91	1.81E-6	3.30E-6	6.01E-6
SK-MEL-2	1.247	2.886	2.853	2.933	2.685	1.221	0.331	98	103	88	-2	-73	2.63E-6	9.48E-6	4.69E-5
SK-MEL-28	0.839	2.540	2.543	2.718	2.582	1.241	0.465	100	110	102	24	-45	4.63E-6	2.22E-5	> 1.00E-4
SK-MEL-5	1.028	3.204	3.140	3.118	2.432	0.028	0.019	97	96	65	-97	-98	1.23E-6	2.50E-6	5.10E-6
UACC-257	0.764	2.132	2.047	2.095	1.869	0.359	0.204	94	97	81	-53	-73	1.70E-6	4.02E-6	9.49E-6
UACC-62	0.978	2.861	2.918	3.044	2.727	0.239	0.292	103	110	93	-76	-70	1.80E-6	3.56E-6	7.05E-6
Ovarian Cancer															
IGROV1	0.412	1.984	1.970	1.855	1.640	0.236	0.182	99	92	78	-43	-56	1.71E-6	4.42E-6	3.52E-5
OVCAR-3	0.511	1.863	1.838	1.936	0.985	0.373	0.121	98	105	35	-27	-76	6.13E-7	3.67E-6	2.93E-5
OVCAR-4	0.631	1.631	1.573	1.595	1.214	0.030	0.006	94	96	58	-95	-99	1.13E-6	2.40E-6	5.07E-6
OVCAR-5	0.576	1.648	1.550	1.590	1.689	0.421	0.073	91	95	104	-27	-87	2.58E-6	6.22E-6	2.41E-5
OVCAR-8	0.342	1.768	1.774	1.774	1.506	0.325	0.013	100	100	82	-5	-96	2.32E-6	8.73E-6	3.10E-5
NCI/ADR-RES	0.682	2.396	2.388	2.451	2.241	0.648	0.693	100	103	91	-5	1	2.67E-6	.	> 1.00E-4
SK-OV-3	0.558	1.690	1.624	1.648	1.599	0.550	0.081	94	96	92	-2	-85	2.81E-6	9.63E-6	3.78E-5
Renal Cancer															
786-0	0.670	2.699	2.596	2.610	2.615	0.972	0.504	95	96	96	15	-25	3.68E-6	2.37E-5	> 1.00E-4
A498	1.579	2.461	2.380	2.380	2.471	1.803	0.036	91	91	101	25	-98	4.72E-6	1.61E-5	4.09E-5
ACHN	0.355	1.655	1.618	1.662	1.504	0.360	0.013	97	101	88	.	-96	2.73E-6	1.01E-5	3.32E-5
CAKI-1	0.878	2.444	2.343	2.350	2.126	1.100	0.201	94	94	80	14	-77	2.84E-6	1.43E-5	5.04E-5
RXF 393	1.198	1.965	1.876	1.899	1.882	1.075	0.301	88	91	89	-10	-75	2.47E-6	7.88E-6	4.12E-5
SN12C	0.754	2.932	2.882	2.865	2.711	0.515	0.077	98	97	90	-32	-90	2.13E-6	5.48E-6	2.06E-5
TK-10	0.792	2.121	2.033	2.096	2.215	1.050	0.380	93	98	107	19	-52	4.48E-6	1.87E-5	9.35E-5
UO-31	0.771	2.208	2.081	2.164	2.102	0.777	0.019	91	97	93	.	-98	2.90E-6	1.01E-5	3.27E-5
Prostate Cancer															
DU-145	0.477	1.878	1.894	1.988	1.926	0.550	0.005	101	108	103	5	-99	3.50E-6	1.12E-5	3.39E-5
Breast Cancer															
MCF7	0.631	3.142	2.862	2.928	2.653	0.250	0.265	89	91	81	-60	-58	1.65E-6	3.73E-6	8.44E-6
MDA-MB-231/ATCC	0.725	1.663	1.713	1.719	1.636	0.721	0.734	105	106	97	.	1	3.03E-6	.	> 1.00E-4
HS 578T	1.104	2.260	2.180	2.272	2.280	1.573	1.063	93	101	102	41	-4	7.00E-6	8.24E-5	> 1.00E-4
BT-549	1.199	2.726	2.589	2.635	2.600	1.576	0.046	91	94	92	25	-96	4.19E-6	1.60E-5	4.15E-5
T-47D	0.489	1.196	1.051	1.090	1.056	0.343	0.217	80	85	80	-30	-56	1.88E-6	5.35E-6	5.99E-5
MDA-MB-468	0.945	1.631	1.598	1.585	1.391	0.326	0.141	95	93	65	-66	-85	1.30E-6	3.15E-6	7.61E-6

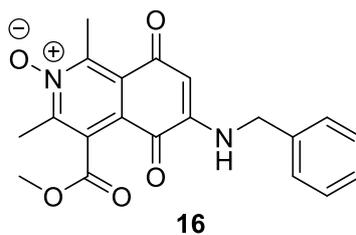
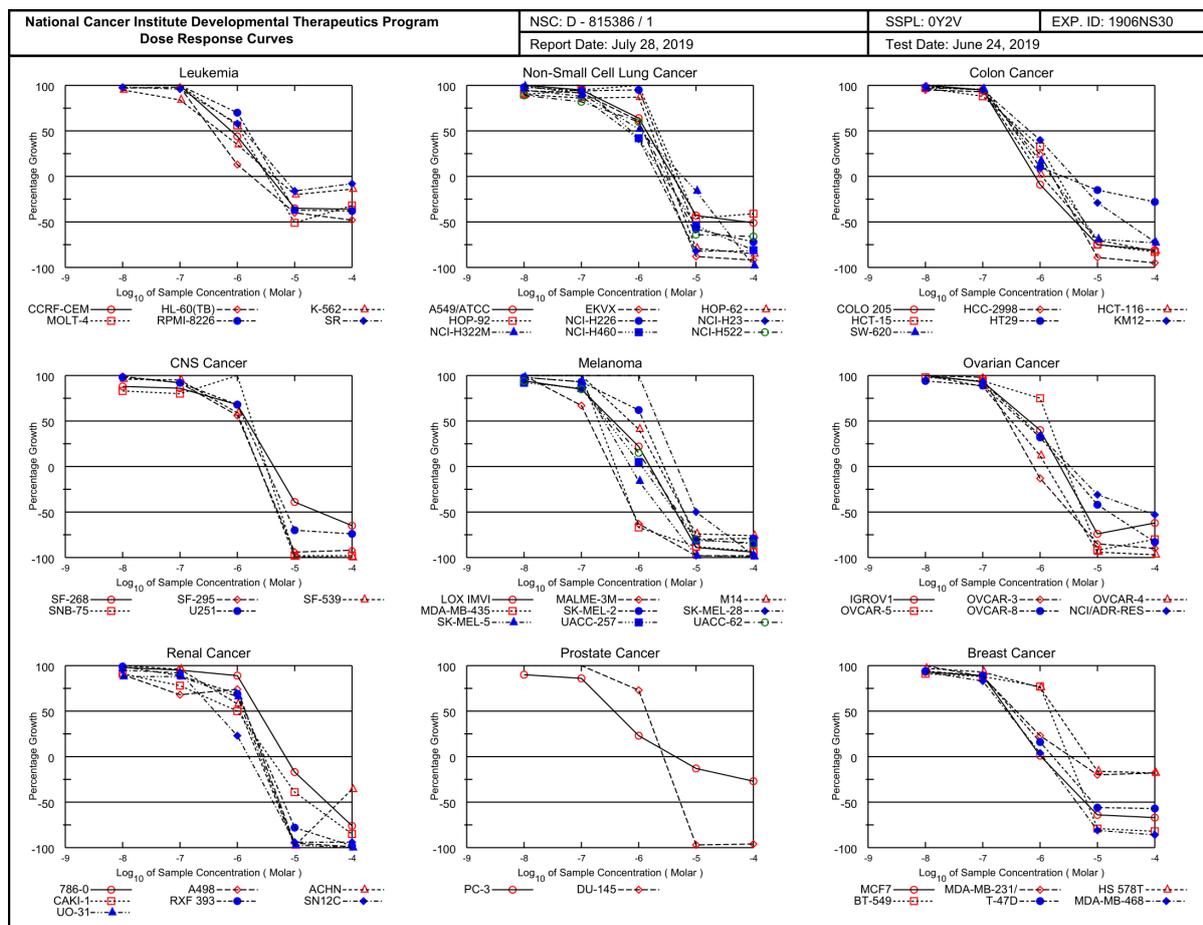
National Cancer Institute Developmental Therapeutics Program		NSC : D - 805946/1		Units :Molar	SSPL:0Y2V	EXP. ID :1809NS03
Mean Graphs		Report Date :October 18, 2018		Test Date :September 17, 2018		
Panel/Cell Line	Log ₁₀ GI50	GI50	Log ₁₀ TGI	TGI	Log ₁₀ LC50	LC50
Leukemia						
OCRF-CEM	-5.53		-4.65		> -4.00	
HL-60(TB)	-5.66		-5.34		> -4.00	
K-562	-5.53		-4.79		> -4.00	
NM1-T4	-5.66		-5.25		> -4.00	
RPMI-8226	-5.56		-4.99		> -4.00	
SR	-5.52		-4.50		> -4.00	
Non-Small Cell Lung Cancer						
A549/ATCC	-5.61		-5.10		-4.18	
ERIX	-5.66		-5.27		-4.54	
HOP-62	-5.51		-4.75		> -4.00	
HOP-82	-5.55		-5.18		-4.25	
NCH-H226	-5.55		-5.00		-4.11	
NCH-H23	-5.69		-5.22		> -4.00	
NCH-H322M	-5.59		-5.09		> -4.00	
NCH-H460	-5.56		-4.86		> -4.00	
NCH-H522	-5.61		-5.12		-4.28	
Colon Cancer						
COLO 205	-6.01		-5.57		-5.14	
HCC-2998	-5.55		-5.10		-4.48	
HCT-116	-5.81		-5.02		-4.47	
HCT-15	-5.77		-5.35		-4.80	
HT29	-5.70		-4.99		> -4.00	
KMT2	-5.62		-5.02		-4.14	
SW-620	-5.51		-4.57		-4.17	
CNS Cancer						
SF-298	-5.55		-5.01		> -4.00	
SF-295	-5.59		-5.13		-4.17	
SF-539	-5.64		-5.28		-4.60	
SNB-19	-5.49		-4.95		-4.45	
SNB-75	-5.44		-4.86		-4.42	
U251	-5.61		-5.15		-4.34	
Melanoma						
LOX IMVI	-5.57		-4.99		-4.18	
MALME-3M	-6.21		-5.73		-5.35	
M14	-5.71		-5.36		-5.02	
MDA-MB-435	-5.74		-5.48		-5.22	
SK-MEL-2	-5.68		-5.02		-4.33	
SK-MEL-28	-5.33		-4.65		> -4.00	
SK-MEL-5	-5.91		-5.60		-5.29	
UACC-257	-5.77		-5.40		-5.02	
UACC-62	-5.75		-5.45		-5.15	
Ovarian Cancer						
IGROV1	-5.77		-5.35		-4.45	
OVCAR-3	-6.21		-5.44		-4.53	
OVCAR-4	-5.95		-5.62		-5.30	
OVCAR-5	-5.89		-5.21		-4.62	
OVCAR-8	-5.64		-5.06		-4.51	
NCIADR-RES	-5.57		-5.06		> -4.00	
SK-OV-3	-5.55		-5.02		-4.42	
Renal Cancer						
785-0	-5.43		-4.63		> -4.00	
A839	-5.33		-4.79		-4.39	
ACHN	-5.56		-5.00		-4.48	
CARI-1	-5.55		-4.85		-4.30	
RXP-393	-5.61		-5.10		-4.39	
SN12C	-5.67		-5.26		-4.69	
TK-10	-5.35		-4.73		-4.03	
UO-31	-5.54		-5.00		-4.49	
Prostate Cancer						
DU-145	-5.46		-4.95		-4.47	
Breast Cancer						
MCF7	-5.78		-5.43		-5.07	
MDA-MB-231/ATCC	-5.52		-5.07		> -4.00	
HS 578T	-5.15		-4.08		> -4.00	
BT 20A	-5.38		-4.80		-4.36	
T-47D	-5.73		-5.27		-4.22	
MDA-MB-468	-5.69		-5.50		-5.12	
MID	-5.62		-5.09		-4.42	
Delta	0.59		0.64		0.93	
Range	1.06		1.65		1.35	



Mean of effective endpoints across 59 cell lines for compound 15 as Log₁₀ Concentration (SD)

GI₅₀ -5.62 (±0.19); TGI -5.09 (±0.3); LC₅₀ -4.42 (±0.41)

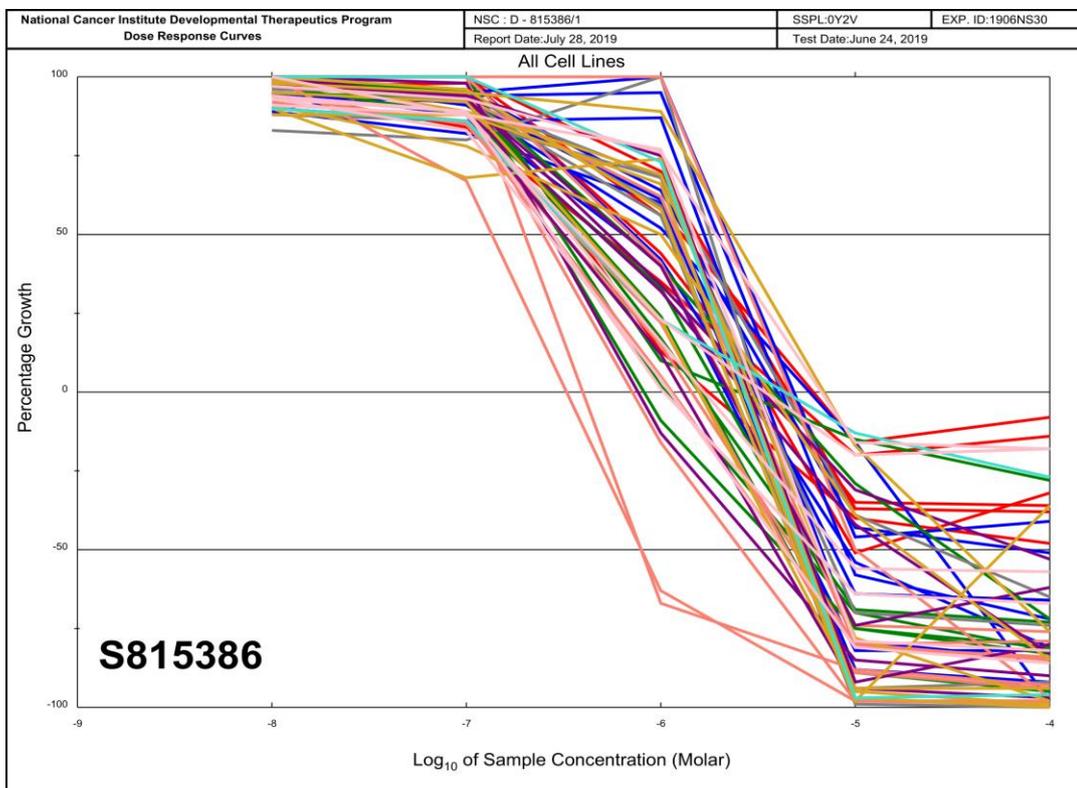
Compound 16



**National Cancer Institute Developmental Therapeutics Program
In-Vitro Testing Results**

NSC : D - 815386 / 1		Experiment ID : 1906NS30					Test Type : 08		Units : Molar						
Report Date : July 28, 2019		Test Date : June 24, 2019					QNS :		MC :						
COMI : RK 6.4.7		Stain Reagent : SRB Dual-Pass Related					SSPL : 0Y2V								
Panel/Cell Line	Time Zero	Log10 Concentration										GI50	TGI	LC50	
		Ctrl	-8.0	-7.0	-6.0	-5.0	-4.0	-8.0	-7.0	-6.0	-5.0				-4.0
Leukemia															
CCRF-CEM	0.555	2.338	2.392	2.432	1.336	0.359	0.357	103	105	44	-35	-36	7.93E-7	3.58E-6	> 1.00E-4
HL-60(TB)	0.970	3.133	3.065	3.081	1.247	0.578	0.503	97	98	13	-40	-48	3.64E-7	1.74E-6	> 1.00E-4
K-562	0.175	1.369	1.308	1.181	0.594	0.140	0.150	95	84	35	-20	-14	4.97E-7	4.30E-6	> 1.00E-4
MOLT-4	0.690	2.474	2.574	2.525	1.687	0.341	0.470	106	103	56	-51	-32	1.14E-6	3.35E-6	.
RPMI-8226	0.896	2.775	2.781	2.774	2.203	0.563	0.555	100	100	70	-37	-38	1.52E-6	4.48E-6	> 1.00E-4
SR	0.401	1.135	1.120	1.109	0.824	0.336	0.367	98	96	58	-16	-8	1.27E-6	6.01E-6	> 1.00E-4
Non-Small Cell Lung Cancer															
A549/ATCC	0.290	1.919	1.913	1.834	1.336	0.167	0.142	100	95	64	-43	-51	1.36E-6	3.99E-6	7.54E-5
EKVX	0.554	1.867	1.788	1.756	1.352	0.067	0.047	94	92	61	-88	-92	1.18E-6	2.56E-6	5.55E-6
HOP-62	0.711	1.813	1.706	1.662	1.668	0.148	0.110	90	86	87	-79	-85	1.67E-6	3.34E-6	6.67E-6
HOP-92	1.036	1.609	1.553	1.582	1.639	0.559	0.614	90	95	105	-46	-41	2.31E-6	4.96E-6	> 1.00E-4
NCI-H226	1.126	2.385	2.357	2.309	2.316	0.474	0.316	98	94	95	-58	-72	1.96E-6	4.17E-6	8.87E-6
NCI-H23	0.613	1.868	1.800	1.717	1.126	0.113	0.110	95	88	41	-82	-82	6.40E-7	2.16E-6	5.52E-6
NCI-H322M	0.743	1.960	1.952	1.849	1.380	0.625	0.015	99	91	52	-16	-98	1.08E-6	5.84E-6	2.60E-5
NCI-H460	0.287	2.764	2.847	2.801	1.325	0.133	0.055	103	101	42	-54	-81	7.31E-7	2.74E-6	9.16E-6
NCI-H522	0.820	2.272	2.117	2.005	1.690	0.294	0.281	89	82	60	-64	-66	1.20E-6	3.04E-6	7.68E-6
Colon Cancer															
COLO 205	0.585	2.203	2.229	2.115	0.533	0.146	0.110	102	95	-9	-75	-81	2.70E-7	8.21E-7	4.17E-6
HCC-2998	0.932	2.543	2.462	2.425	1.325	0.107	0.045	95	93	24	-89	-95	4.21E-7	1.64E-6	4.55E-6
HCT-116	0.244	2.059	2.024	1.968	0.283	0.072	0.044	98	95	2	-70	-82	3.05E-7	1.07E-6	5.22E-6
HCT-15	0.278	2.113	2.060	1.885	0.877	0.069	0.047	97	88	33	-75	-83	4.83E-7	2.01E-6	5.84E-6
HT29	0.208	1.712	1.717	1.761	0.364	0.178	0.150	100	103	10	-15	-28	3.74E-7	2.60E-6	> 1.00E-4
KM12	0.579	2.965	2.950	2.834	1.530	0.410	0.162	99	95	40	-29	-72	6.53E-7	3.77E-6	3.05E-5
SW-620	0.258	1.891	1.836	1.829	0.539	0.080	0.070	97	96	17	-69	-73	3.85E-7	1.58E-6	6.00E-6
CNS Cancer															
SF-268	0.838	2.441	2.244	2.221	1.930	0.515	0.295	88	86	68	-39	-65	1.48E-6	4.35E-6	2.72E-5
SF-295	0.781	2.926	2.904	2.764	1.980	0.049	0.060	99	92	56	-94	-92	1.09E-6	2.36E-6	5.10E-6
SF-539	1.054	2.819	2.745	2.732	2.089	0.013	0.004	96	95	59	-99	-100	1.13E-6	2.36E-6	4.90E-6
SNB-75	1.027	1.811	1.679	1.656	1.820	0.019	0.025	83	80	101	-98	-98	1.81E-6	3.22E-6	5.73E-6
U251	0.272	1.582	1.550	1.475	1.157	0.082	0.071	98	92	68	-70	-74	1.34E-6	3.10E-6	7.15E-6
Melanoma															
LOX IMVI	0.496	2.775	2.644	2.429	1.002	0.054	0.031	94	85	22	-89	-94	3.60E-7	1.58E-6	4.45E-6
MALME-3M	0.763	1.675	1.672	1.371	0.280	0.013	0.015	100	67	-63	-98	-98	1.34E-7	3.26E-7	7.89E-7
M14	0.430	1.807	1.840	1.940	0.988	0.113	0.104	102	110	41	-74	-76	7.29E-7	2.26E-6	6.19E-6
MDA-MB-435	0.512	2.664	2.692	2.765	0.170	0.061	0.036	101	105	-67	-88	-93	2.08E-7	4.08E-7	7.98E-7
SK-MEL-2	1.127	2.562	2.536	2.466	2.016	0.221	0.233	98	93	62	-80	-79	1.21E-6	2.72E-6	6.12E-6
SK-MEL-28	0.772	1.914	1.979	2.042	1.942	0.390	0.027	106	111	102	-50	-97	2.21E-6	4.72E-6	1.02E-5
SK-MEL-5	0.784	3.159	3.121	3.004	0.657	0.020	0.007	98	93	-16	-98	-99	2.49E-7	7.12E-7	2.60E-6
UACC-257	0.739	1.905	1.816	1.746	0.796	0.139	0.115	92	86	5	-81	-84	2.79E-7	1.14E-6	4.33E-6
UACC-62	0.975	2.652	2.555	2.401	1.227	0.193	0.143	94	85	15	-80	-85	3.16E-7	1.44E-6	4.82E-6
Ovarian Cancer															
IGROV1	0.547	2.134	2.177	2.020	1.188	0.144	0.206	103	93	40	-74	-62	6.56E-7	2.26E-6	6.19E-6
OVCAR-3	0.469	1.531	1.602	1.511	0.410	0.070	0.048	107	98	-13	-85	-90	2.72E-7	7.70E-7	3.28E-6
OVCAR-4	0.560	1.500	1.496	1.384	0.676	0.031	0.018	100	88	12	-94	-97	3.16E-7	1.30E-6	3.83E-6
OVCAR-5	0.600	1.584	1.569	1.522	1.334	0.046	0.118	98	94	75	-92	-80	1.40E-6	2.80E-6	5.58E-6
OVCAR-8	0.444	2.368	2.252	2.151	1.063	0.256	0.075	94	89	32	-42	-83	4.84E-7	2.70E-6	1.53E-5
NCI/ADR-RES	0.563	2.074	2.091	1.970	1.076	0.387	0.266	101	93	34	-31	-53	5.35E-7	3.31E-6	7.38E-5
Renal Cancer															
786-0	0.921	2.757	2.719	2.670	2.556	0.762	0.222	98	95	89	-17	-76	2.33E-6	6.88E-6	3.61E-5
A498	1.553	2.098	2.041	1.921	1.957	0.073	0.010	90	68	74	-95	-99	1.39E-6	2.74E-6	5.40E-6
ACHN	0.354	1.569	1.597	1.521	1.065	0.008	0.228	102	96	58	-98	-36	1.13E-6	2.37E-6	.
CAKI-1	0.772	2.673	2.506	2.258	1.716	0.475	0.117	91	78	50	-39	-85	9.72E-7	3.66E-6	1.77E-5
RXF 393	0.883	1.677	1.668	1.589	1.429	0.193	0.018	99	89	69	-78	-98	1.34E-6	2.94E-6	6.43E-6
SN12C	0.558	1.964	1.894	1.858	0.881	0.034	0.033	95	92	23	-94	-94	4.08E-7	1.57E-6	4.21E-6
UO-31	0.542	1.595	1.465	1.465	1.239	0.015	-0.001	88	88	66	-97	-100	1.26E-6	2.54E-6	5.13E-6
Prostate Cancer															
PC-3	0.573	1.664	1.551	1.511	0.819	0.497	0.420	90	86	23	-13	-27	3.69E-7	4.26E-6	> 1.00E-4
DU-145	0.410	1.710	1.774	1.764	1.359	0.014	0.017	105	104	73	-97	-96	1.37E-6	2.69E-6	5.31E-6
Breast Cancer															
MCF7	0.467	2.487	2.350	2.268	0.497	0.170	0.154	93	89	1	-64	-67	2.80E-7	1.05E-6	6.18E-6
MDA-MB-231/ATCC	0.775	1.855	1.871	1.727	1.024	0.617	0.636	102	88	23	-20	-18	3.85E-7	3.38E-6	> 1.00E-4
HS 578T	0.869	1.941	1.911	1.861	1.679	0.730	0.709	97	93	76	-16	-18	1.90E-6	6.68E-6	> 1.00E-4
BT-549	1.031	2.013	1.927	1.897	1.790	0.213	0.184	91	88	77	-79	-82	1.49E-6	3.12E-6	6.50E-6
T-47D	0.723	1.736	1.680	1.629	0.889	0.317	0.308	94	89	16	-56	-57	3.46E-7	1.68E-6	8.21E-6
MDA-MB-468	0.732	1.442	1.390	1.319	0.758	0.137	0.106	93	83	4	-81	-86	2.59E-7	1.10E-6	4.28E-6

National Cancer Institute Developmental Therapeutics Program		NSC : D - 815386/1		Units :Molar		SSPL :0Y2V		EXP. ID :1906NS30	
Mean Graphs		Report Date :July 28, 2019		Test Date :June 24, 2019					
Panel/Cell Line	Log ₁₀ GI50	GI50	Log ₁₀ TGI	TGI	Log ₁₀ LC50	LC50			
Leukemia									
CCRF-CEM	-6.10		-5.45		>	>	>	>	>
HL-60(TB)	-6.44		-5.76		>	>	>	>	>
K-562	-6.30		-5.37		>	>	>	>	>
MOLT-4	-6.36		-5.48		>	>	>	>	>
RPMI-8226	-5.92		-5.35		>	>	>	>	>
SR	-5.90		-5.22		>	>	>	>	>
Non-Small Cell Lung Cancer									
A549(ATCC)	-5.87		-5.40						
ERVX	-5.53		-5.59						
HOP-82	-5.78		-5.48						
HOP-92	-5.64		-5.30						
NCI-H226	-5.71		-5.38						
NCI-H23	-6.19		-5.67						
NCI-H322M	-5.97		-5.23						
NCI-H460	-6.14		-5.96						
NCI-H522	-5.92		-5.82						
Colon Cancer									
COLO 205	-6.57		-6.09						
HCC-2998	-6.56		-5.75						
HCT-119	-6.52		-5.97						
HCT-15	-6.32		-5.70						
HT29	-6.43		-5.59						
KM12	-6.19		-5.42						
SW-620	-6.41		-5.80						
CNS Cancer									
U251	-5.83		-5.51						
SF-298	-5.96		-5.63						
SF-295	-5.96		-5.63						
SF-539	-5.95		-5.63						
SNB-75	-5.74		-5.49						
U251	-5.87		-5.51						
Melanoma									
LOX IMVI	-6.44		-5.80						
MALME-3M	-6.87		-5.49						
M14	-6.14		-5.65						
MDA-MB-435	-6.68		-6.39						
SK-MEL-2	-5.92		-5.56						
SK-MEL-28	-5.85		-5.33						
SK-MEL-5	-6.60		-6.15						
UACC-297	-6.55		-5.94						
UACC-62	-6.50		-5.84						
Ovarian Cancer									
IGROV1	-6.18		-5.65						
OVCAR-3	-6.57		-6.11						
OVCAR-4	-6.50		-5.88						
OVCAR-5	-6.55		-5.55						
OVCAR-8	-6.32		-5.57						
NCI/ADR-RES	-6.27		-5.48						
Renal Cancer									
786-O	-5.63		-5.16						
A498	-5.86		-5.56						
ACHN	-5.55		-5.63						
CAKI-1	-6.01		-5.44						
RXF 393	-5.87		-5.53						
SN12C	-6.39		-5.80						
UO-31	-5.90		-5.60						
Prostate Cancer									
PC-3	-6.43		-5.37						
DU-145	-5.86		-5.57						
Breast Cancer									
MCF-7	-6.55		-5.96						
MDA-MB-231(ATCC)	-6.21		-5.47						
HS 578T	-5.73		-5.18						
BT 20	-6.53		-5.51						
T-47D	-6.46		-5.77						
MDA-MB-468	-6.59		-5.96						
MID	-6.15		-5.63						
Delta	0.72		0.86						
Range	1.24		1.33						



Mean of effective endpoints across 59 cell lines for compound 16 as Log₁₀ Concentration (SD)

GI₅₀ -6.15 (±0.34); TGI -5.63 (±0.31); LC₅₀ -4.95 (±0.6)

Calculation of Mean GI₅₀ and Trends

Mean GI₅₀ was calculated from 53 human cancer cell lines that were common across the four compounds **3**, **11**, **15** and **18**. Conditional formatting was applied to the GI₅₀ values per compound row with the colour green representing more un-responsive cell lines and red representing more-responsive cell lines.

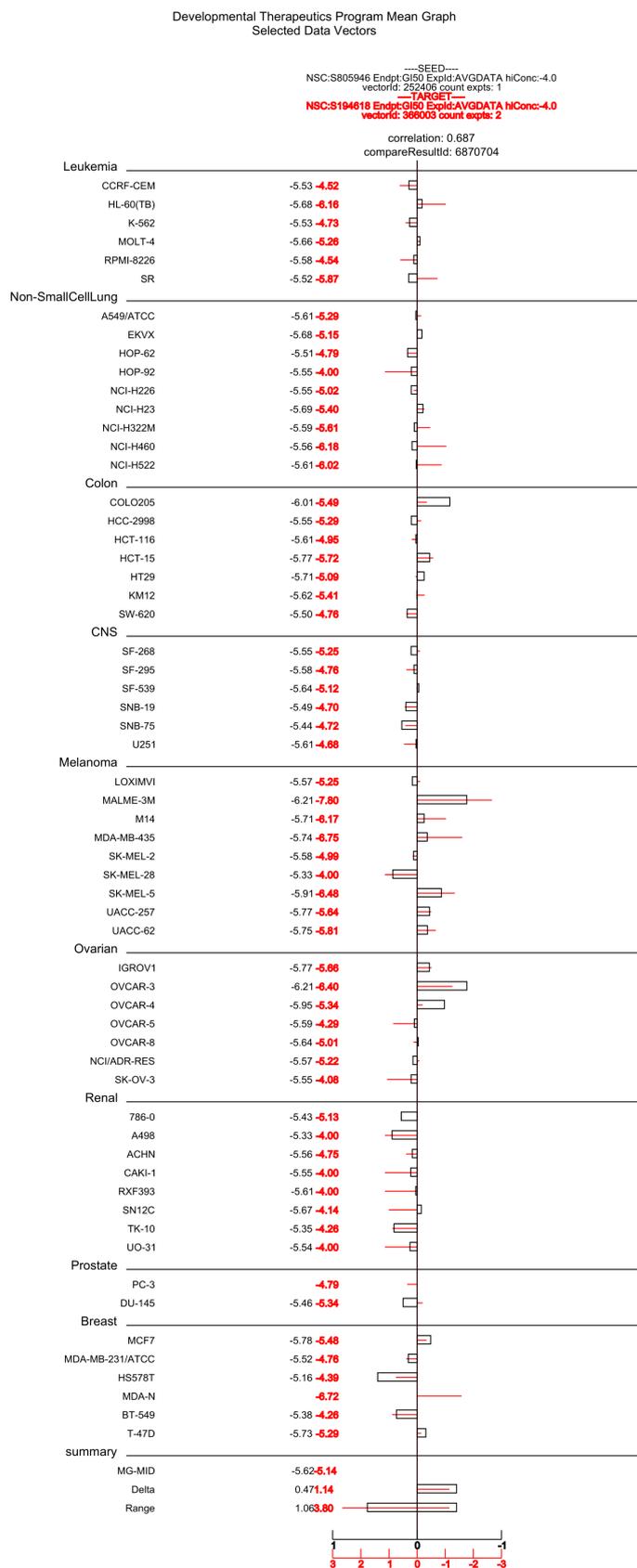
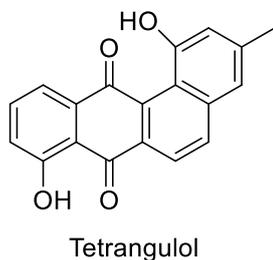
	3	11	15	18
CCRF-CEM	0.0559	3.11	2.98	0.793
K-562	3.04	3.36	2.94	0.497
MOLT-4	1.69	3.09	2.21	1.14
RPMI-8226	2.07	3.24	2.61	1.52
AS49/ATCC	3.12	2.56	2.47	1.36
EKVX	2.02	2.12	2.09	1.18
HOP-62	0.744	3.12	3.1	1.67
HOP-92	2.12	2.46	2.8	2.31
NCI-H226	1.42	4.01	2.81	1.96
NCI-H23	1.63	1.89	2.03	0.64
NCI-H322M	1.68	3.45	2.59	1.08
NCI-H460	2.72	2.94	2.74	0.731
NCI-H522	1.66	2.25	2.45	1.2
COLO-205	1.64	1.7	0.977	0.27
HCC-2998	1.64	3.4	2.8	0.421
HCT-116	0.945	2.5	2.47	0.305
HCT-15	1.43	2.76	1.7	0.483
HT-29	2.41	2.97	1.97	0.374
KM12	1.99	2.93	2.4	0.653
SW-620	1.54	3.39	3.12	0.385
SF-268	2.05	3.46	2.81	1.48
SF-295	1.78	3.04	2.6	1.09
SF-539	1.8	2.85	2.29	1.13
U251	1.48	2.74	2.46	1.34
LOX IMVI	1.44	2.45	2.72	0.36
MALME-3M	1.53	1.47	0.617	0.134
M14	1.78	2.06	1.97	0.729
MDA-MB-435	1.79	1.86	1.81	0.208
SK-MEL-2	1.89	2.52	2.63	1.21
SK-MEL-28	1.96	5.79	4.63	2.21
SK-MEL-5	1.14	1.47	1.23	0.249
UACC-257	1.57	1.62	1.7	0.279
UACC-62	1.63	1.41	1.8	0.316
IGROV1	1.74	2.05	1.71	0.656
OVCAR-3	0.314	2.27	0.613	0.272
OVCAR-4	1.2	1.55	1.13	0.316
OVCAR-5	1.76	3.11	2.58	1.4
OVCAR-8	0.339	2.51	2.32	0.484
NCI-ADR/RES	2.33	2.83	2.67	0.535
786-0	2.07	4.65	3.68	2.33
A498	3.58	4.48	4.72	1.39
ACHN	1.9	3.08	2.73	1.13
CAKI-1	1.95	5.66	2.84	0.972
RXF 393	1.42	3.08	2.47	1.34
SN12C	1.62	1.49	2.13	0.408
UO-31	1.69	2.41	2.9	1.26
DU-145	1.82	4.26	3.5	1.37
MCF7	1.55	1.3	1.65	0.29
MDA-MB-231/ATCC	2.68	2.11	3.03	0.385
HS 578T	2.84	10.8	7	1.9
BT-549	1.72	4.08	4.19	1.49
T-47D	1.97	2.26	1.88	0.346
MDA-MB-468	0.946	1.1	1.3	0.259
Mean GI ₅₀	1.75	2.93	2.52	0.91

Mean LC₅₀ was calculated from 50 human cancer cell lines that were common across the four compounds **3,11,15** and **16**. Conditional formatting was applied to the GI₅₀ values per compound row with the colour green representing more un-responsive cell lines and red representing more-responsive cell lines.

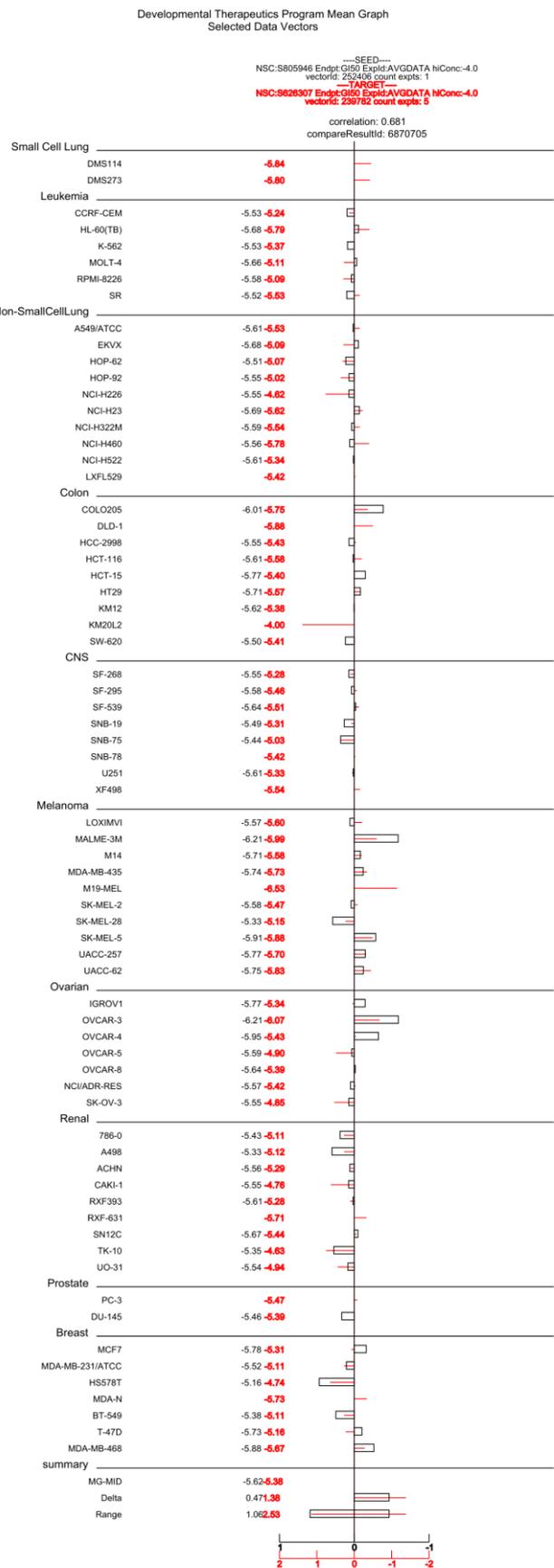
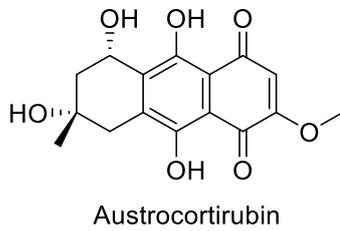
	3	11	15	16
CCRF-CEM	100	100	100	100
K-562	100	100	100	100
RPMI-8226	100	100	100	100
A549/ATCC	55.3	43.5	66.1	75.4
EKVX	22.2	24.4	28.7	5.55
HOP-62	5.79	33.5	100	6.67
HOP-92	23.8	22.7	56.5	100
NCI-H226	6.26	74.9	77.8	8.87
NCI-H23	100	100	100	5.52
NCI-H322M	5.62	33.4	100	26
NCI-H460	49.9	63.7	100	9.16
NCI-H522	8.11	29.8	52.9	7.68
COLO-205	6.85	7.73	7.19	4.17
HCC-2998	5.95	40	32.8	4.55
HCT-116	46	27.5	34.2	5.22
HCT-15	7.69	30.1	15.7	5.84
HT-29	100	100	100	100
KM12	15.1	62.2	73.1	30.5
SW-620	9.09	42.8	67	6
SF-268	27.6	54.1	100	27.2
SF-295	6.28	34.3	67.4	5.1
SF-539	5.68	28.4	15.8	4.9
U251	5.4	31.9	46	7.15
LOX IMVI	6.42	79.1	66.2	4.45
MALME-3M	5.57	5.55	4.43	0.789
M14	6.69	13.8	9.58	6.19
MDA-MB-435	6.13	6.15	6.01	0.798
SK-MEL-2	8.41	29.5	46.9	6.12
SK-MEL-28	6.62	44.2	100	10.2
SK-MEL-5	5.07	5.54	5.1	2.6
UACC-257	7.11	6.3	9.49	4.33
UACC-62	6.3	6.12	7.05	4.82
IGROV1	11.8	29.2	35.2	6.19
OVCAR-3	22.2	24.6	29.3	3.28
OVCAR-4	5.08	5.8	5.07	3.83
OVCAR-5	5.91	33.4	24.1	5.58
OVCAR-8	4.54	76.8	31	15.3
NCI-ADR/RES	100	100	100	73.8
786-0	9.84	41.1	100	36.1
A498	38.1	42.2	40.9	5.4
CAKI-1	9.05	44	50.4	17.7
RXF 393	5.84	35.7	41.2	6.43
SN12C	5.93	8	20.6	4.21
UO-31	6.8	33	32.7	5.13
DU-145	5.69	38.5	33.9	5.31
MDA-MB-231/ATCC	100	33.3	100	100
HS 578T	100	100	100	100
BT-549	5.73	40.1	41.5	6.5
T-47D	100	33.7	59.9	8.21
MDA-MB-468	7.48	6.87	7.61	4.28
Mean LC ₅₀	28.3	42.14	52.99	23.86

COMPARE Analysis

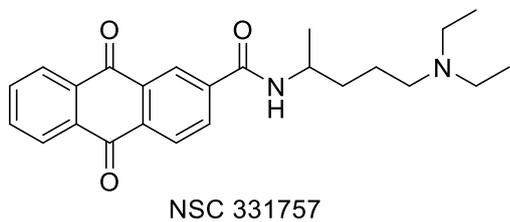
Correlation of 15 - Tetrangulol



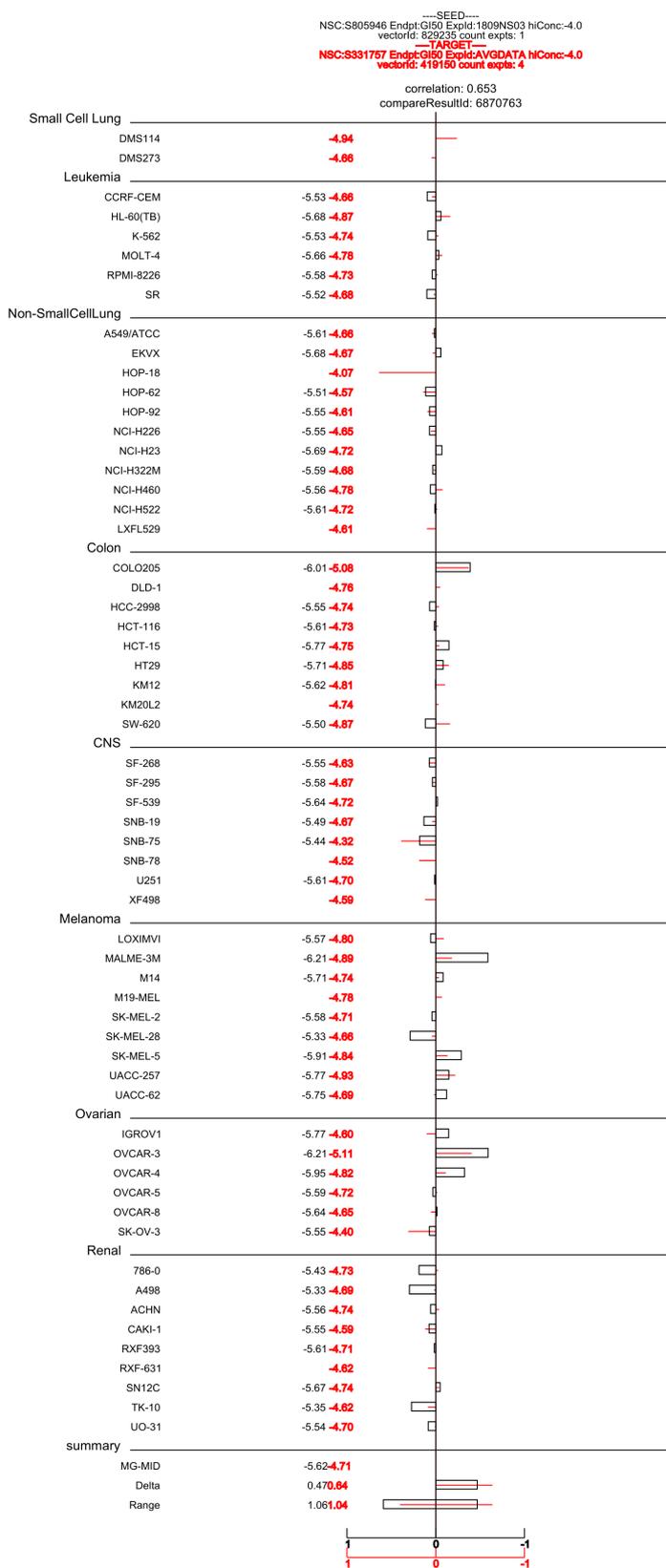
Correlation of 15 - (1S,3S)-austrocortirubin



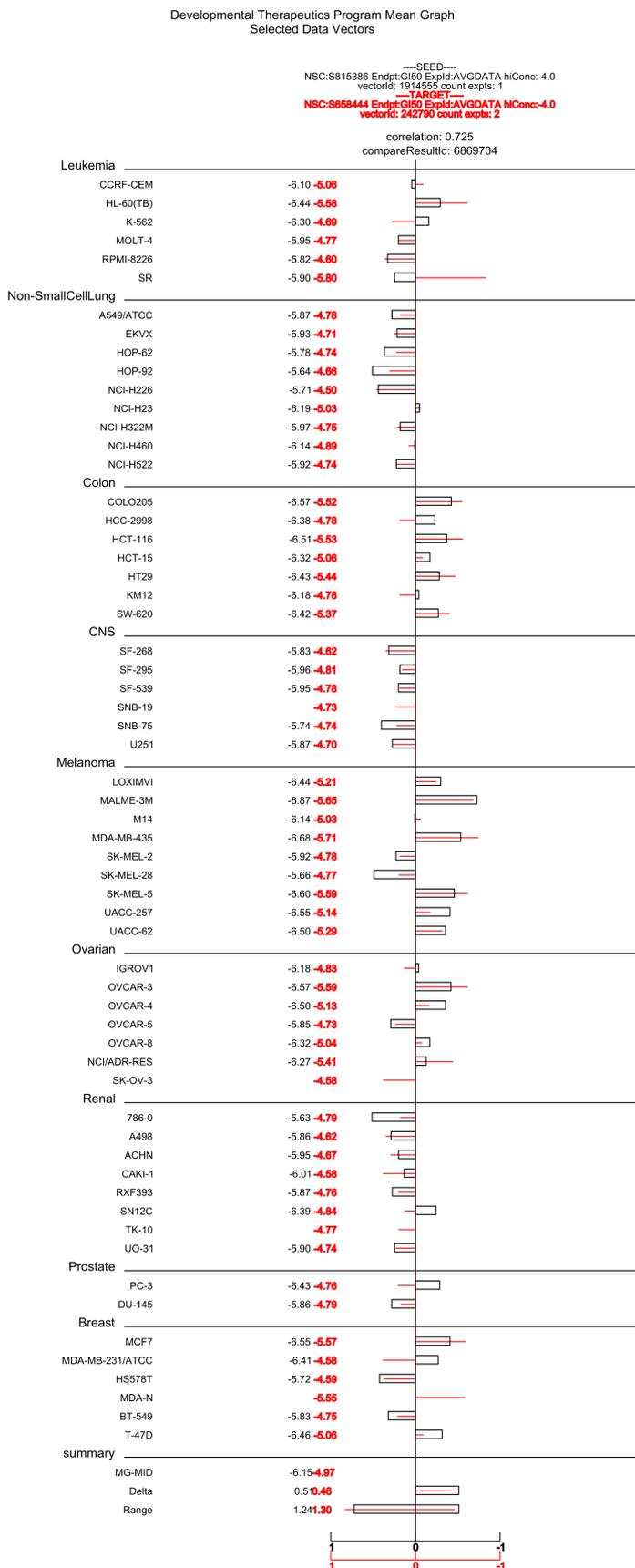
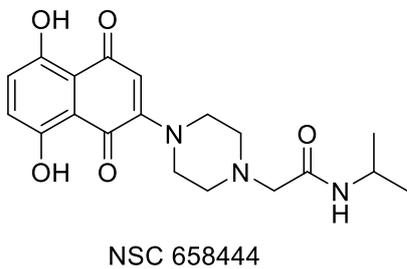
Correlation of 15 – NSC 331757



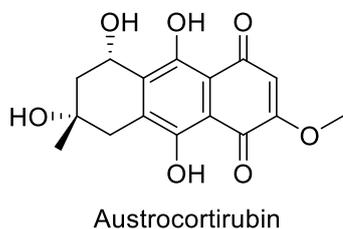
Developmental Therapeutics Program Mean Graph
Selected Data Vectors



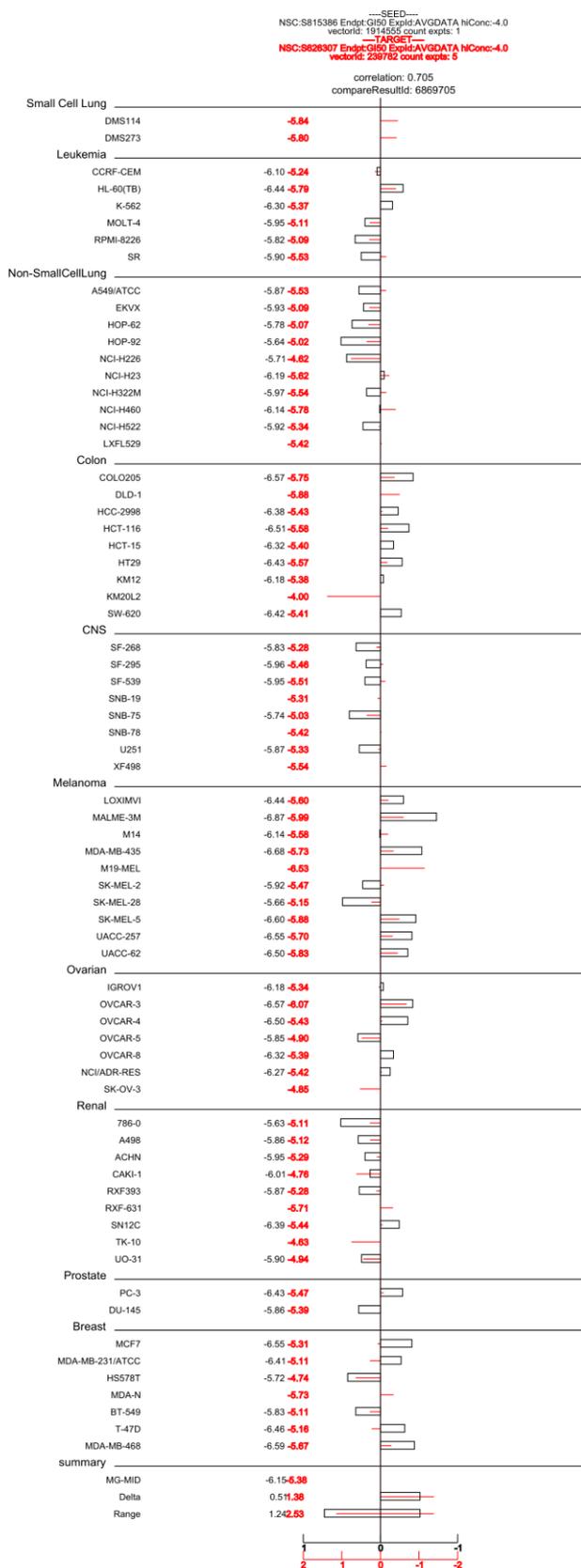
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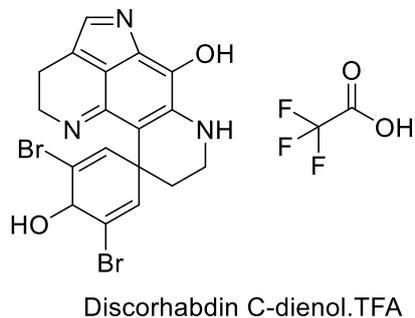
Correlation of 16 - (1S,3S)-austrocrotirubin



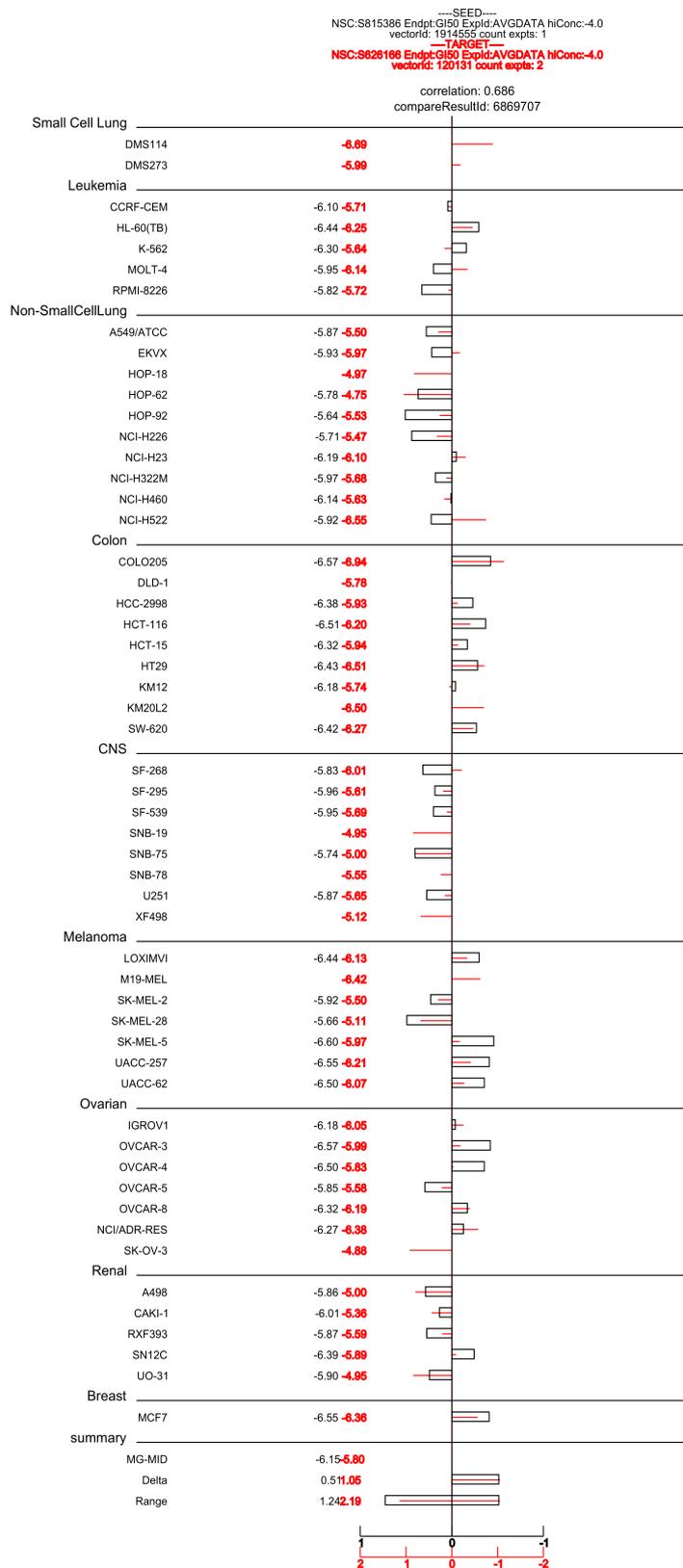
Developmental Therapeutics Program Mean Graph
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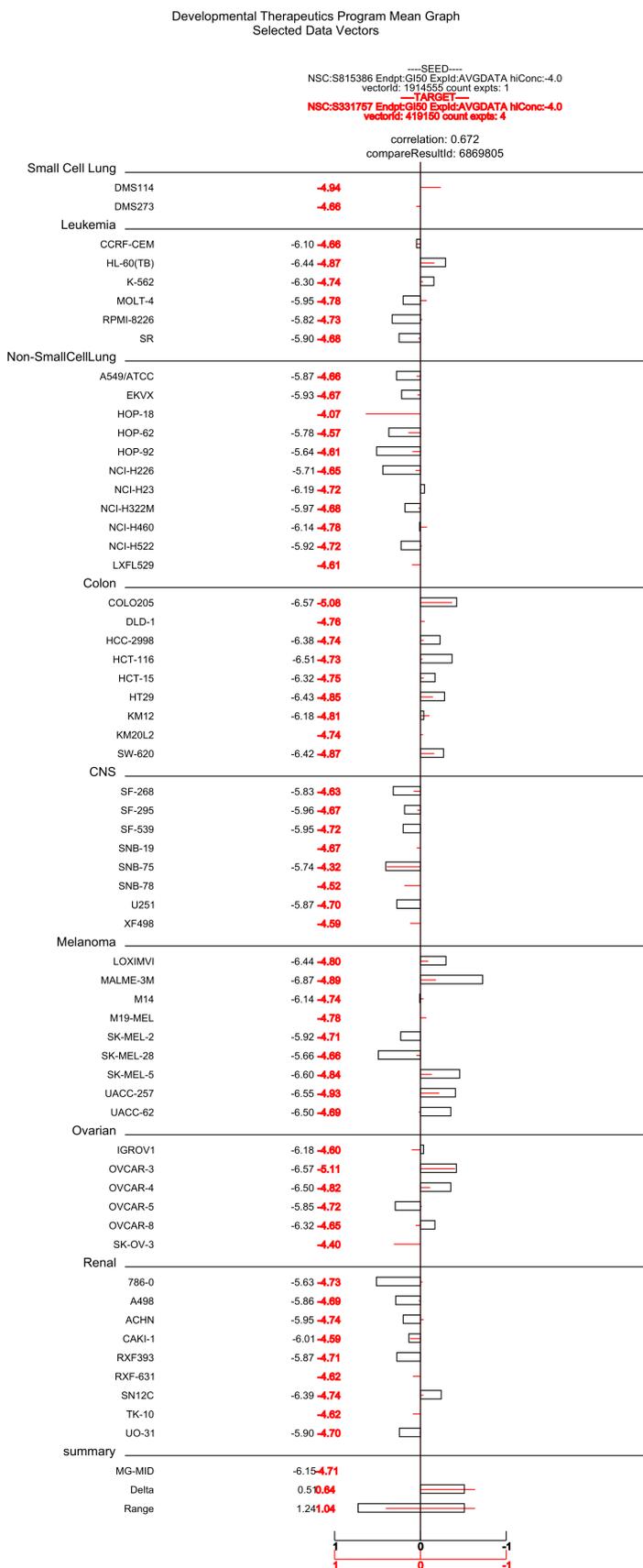
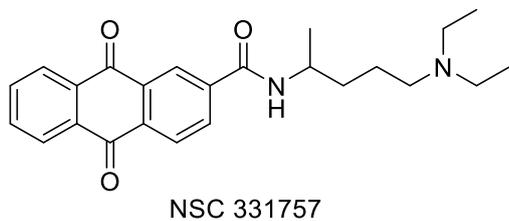
Correlation of 16 – Discorhabdin C-dienol.TFA



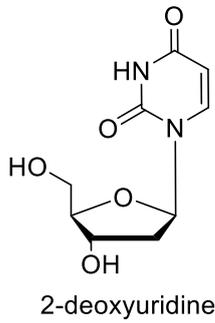
Developmental Therapeutics Program Mean Graph
Selected Data Vectors



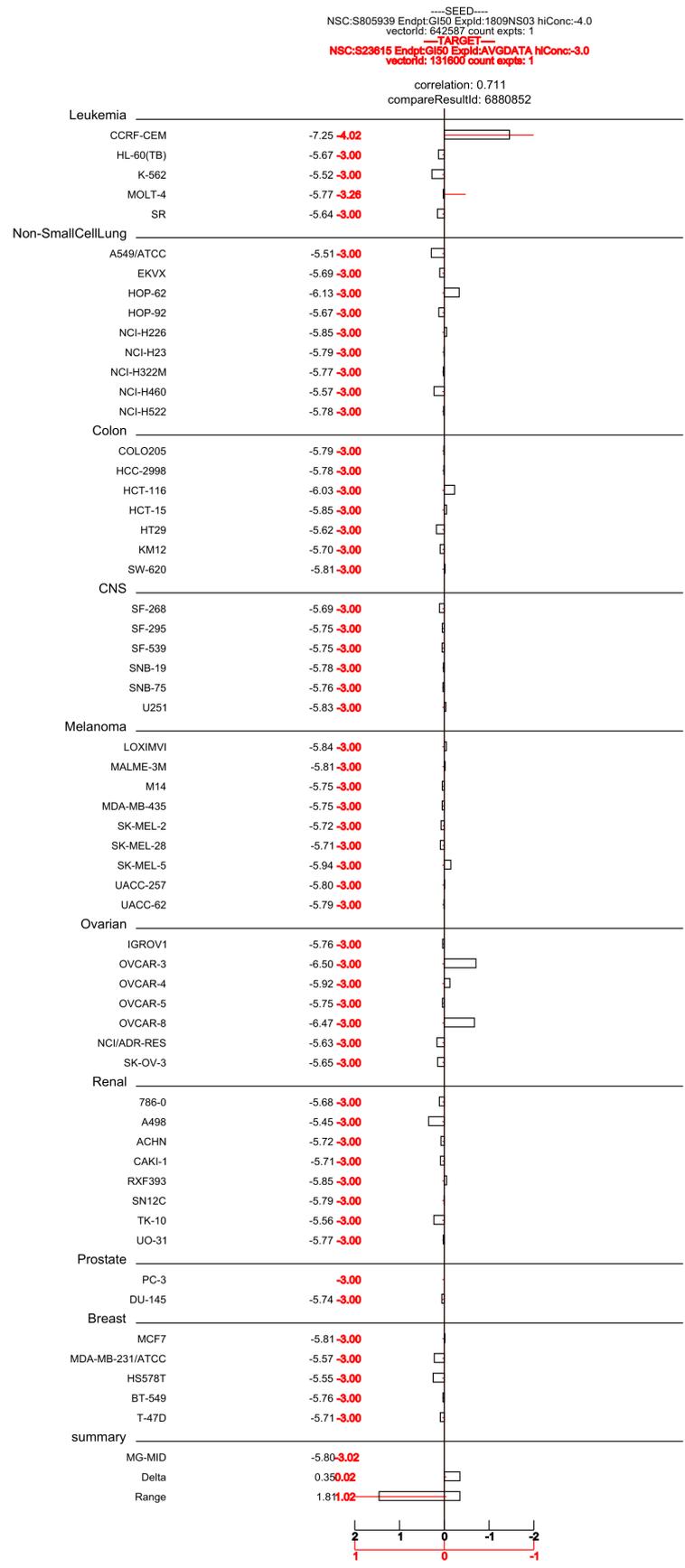
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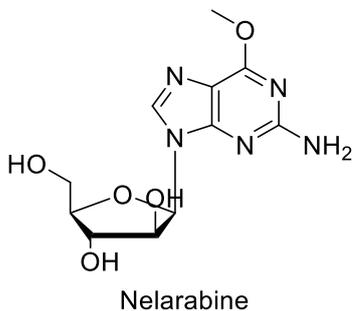
Correlation of 3 – 2-Deoxyuridine



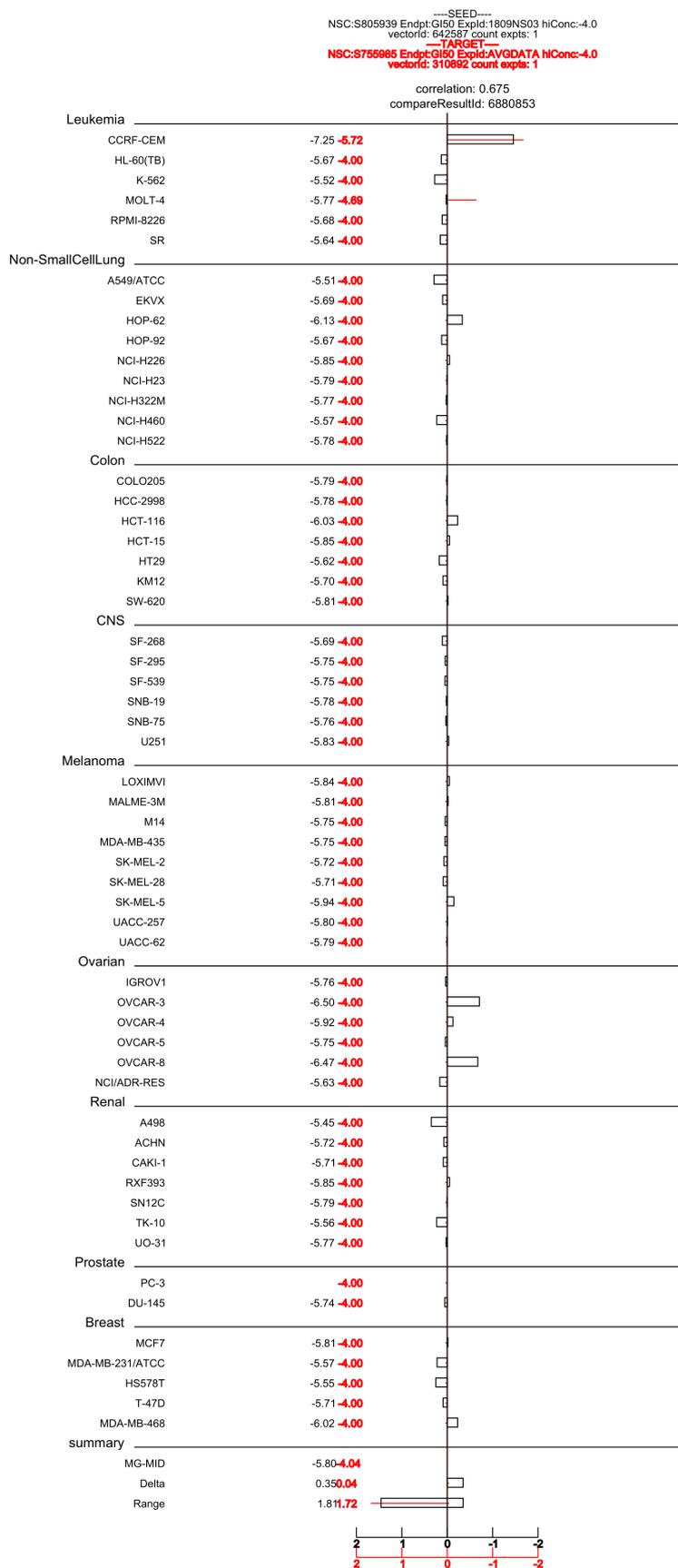
Developmental Therapeutics Program Mean Graph Selected Data Vectors



Correlation of 3- Nelarabine



Developmental Therapeutics Program Mean Graph Selected Data Vectors



Matrix COMPARE of **15** (NSC 805946) and **16** (NSC 815386)

Row Label	829235 NSC:S805946 Endpt:GI50 Expld:1809NS03 hiConc:-4.0 null	1914555 NSC:S815386 Endpt:GI50 Expld:AVGDATA hiConc:-4.0 null
829235 NSC:S805946 Endpt:GI50 Expld:1809NS03 hiConc:-4.0 null	correlation: 1.0 count cell lines: 59 seed stdDev: 0.185 target stdDev: 0.185 <input type="checkbox"/> Select this result	correlation: 0.725 count cell lines: 56 seed stdDev: 0.185 target stdDev: 0.319 <input type="checkbox"/> Select this result
1914555 NSC:S815386 Endpt:GI50 Expld:AVGDATA hiConc:-4.0 null	correlation: 0.725 count cell lines: 56 seed stdDev: 0.319 target stdDev: 0.185 <input type="checkbox"/> Select this result	correlation: 1.0 count cell lines: 57 seed stdDev: 0.319 target stdDev: 0.319 <input type="checkbox"/> Select this result

Matrix COMPARE of **15** (NSC 805946) and **3** (NSC 805939)

Row Label	252406 NSC:S805946 Endpt:GI50 Expld:AVGDATA hiConc:-4.0 null	642587 NSC:S805939 Endpt:GI50 Expld:1809NS03 hiConc:-4.0 null
252406 NSC:S805946 Endpt:GI50 Expld:AVGDATA hiConc:-4.0 null	correlation: 1.0 count cell lines: 59 seed stdDev: 0.185 target stdDev: 0.185 <input type="checkbox"/> Select this result	correlation: 0.291 count cell lines: 59 seed stdDev: 0.185 target stdDev: 0.263 <input type="checkbox"/> Select this result
642587 NSC:S805939 Endpt:GI50 Expld:1809NS03 hiConc:-4.0 null	correlation: 0.291 count cell lines: 59 seed stdDev: 0.263 target stdDev: 0.185 <input type="checkbox"/> Select this result	correlation: 1.0 count cell lines: 59 seed stdDev: 0.263 target stdDev: 0.263 <input type="checkbox"/> Select this result

Graph selected matrix COMPARE results

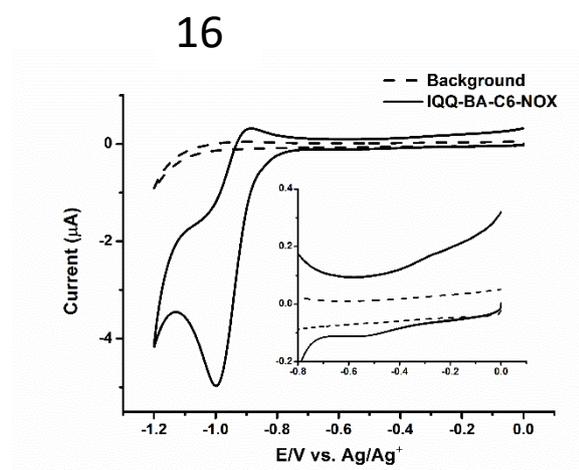
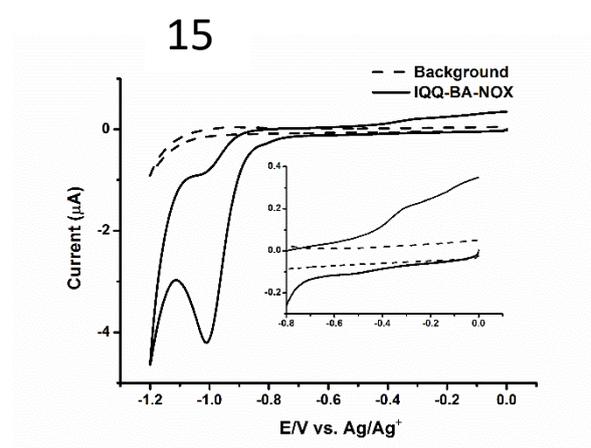
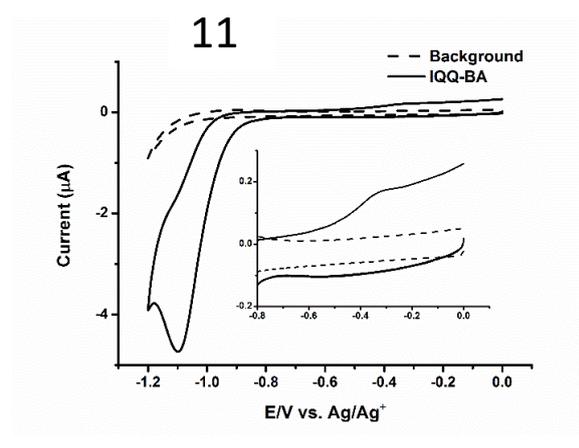
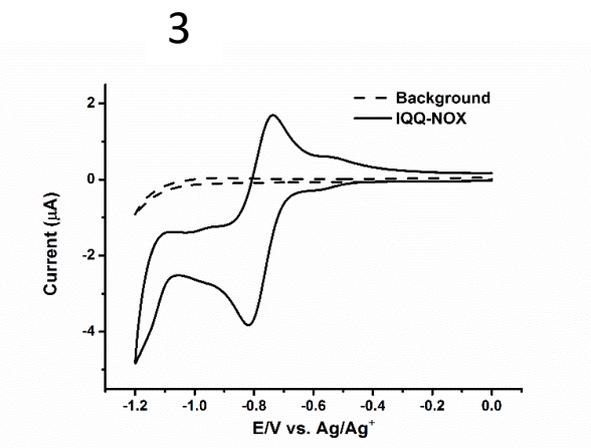
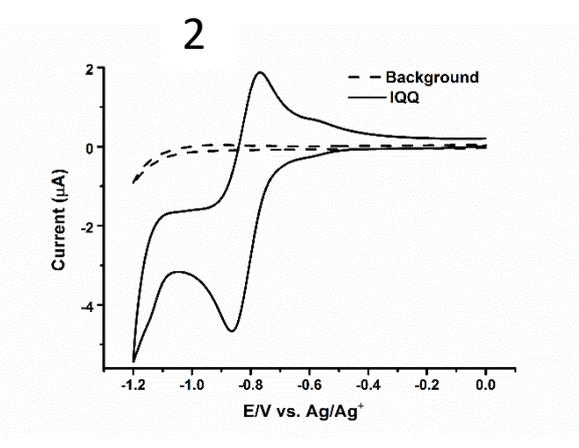
Matrix COMPARE of **16** (NSC 815386) and **3** (NSC 805939)

Row Label	642587 NSC:S805939 Endpt:GI50 Expld:1809NS03 hiConc:-4.0 null	1914555 NSC:S815386 Endpt:GI50 Expld:AVGDATA hiConc:-4.0 null
642587 NSC:S805939 Endpt:GI50 Expld:1809NS03 hiConc:-4.0 null	correlation: 1.0 count cell lines: 59 seed stdDev: 0.263 target stdDev: 0.263 <input type="checkbox"/> Select this result	correlation: 0.2 count cell lines: 56 seed stdDev: 0.268 target stdDev: 0.319 <input type="checkbox"/> Select this result
1914555 NSC:S815386 Endpt:GI50 Expld:AVGDATA hiConc:-4.0 null	correlation: 0.2 count cell lines: 56 seed stdDev: 0.319 target stdDev: 0.268 <input type="checkbox"/> Select this result	correlation: 1.0 count cell lines: 57 seed stdDev: 0.319 target stdDev: 0.319 <input type="checkbox"/> Select this result

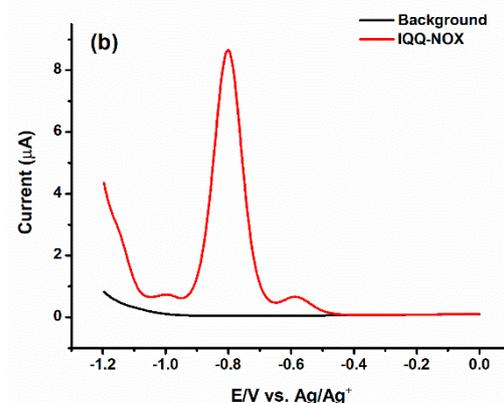
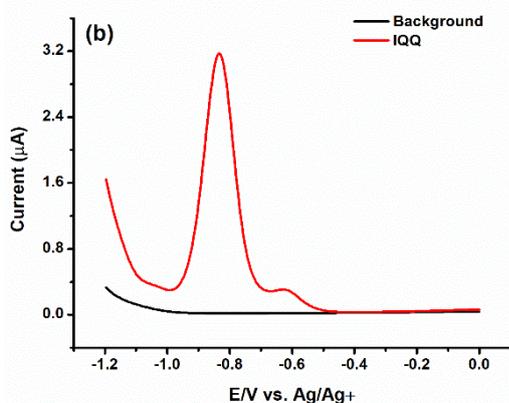
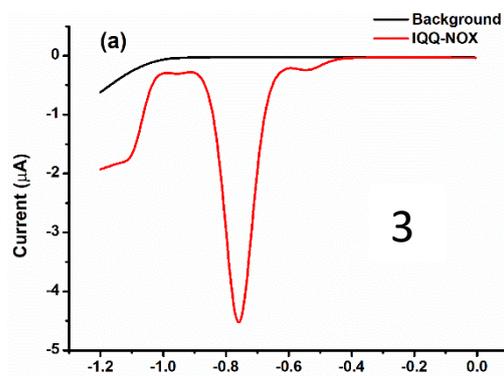
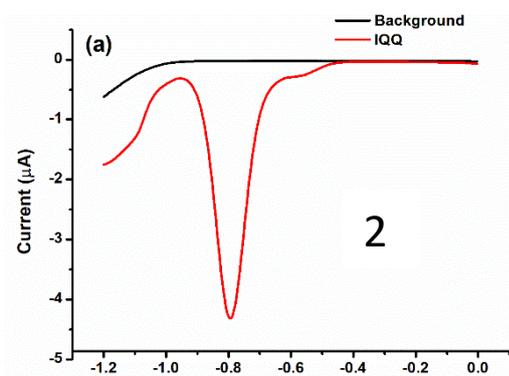
Graph selected matrix COMPARE results

Electrochemical Graphs

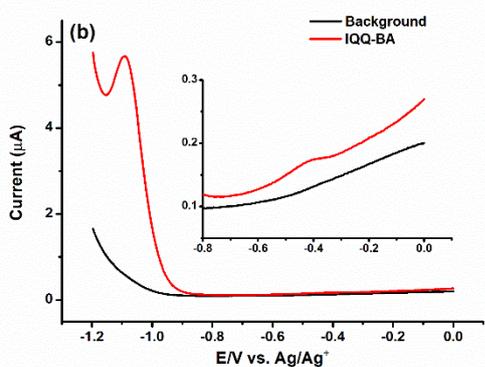
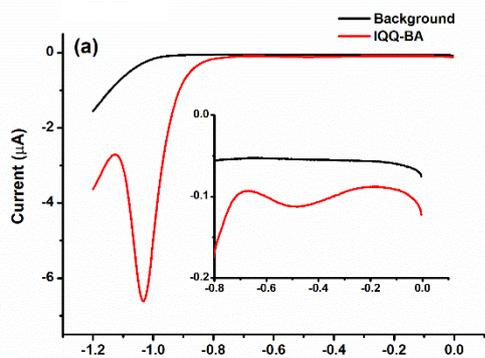
CV of 2 mM **2**, 2 mM **3**, 2 mM **11**, 2 mM **15**, and 3 mM **16** obtained by a Pt electrode vs. Ag/Ag⁺ using 0.1 M of tetrabutylammonium tetrafluoroborate in ACN, a scan rate of 100 mVs⁻¹.



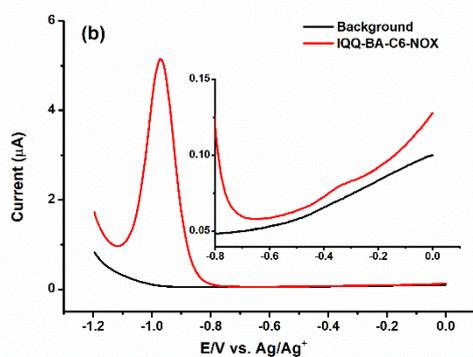
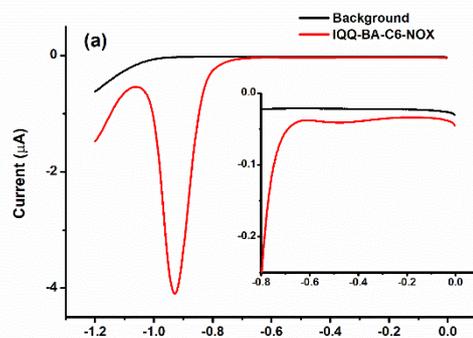
Squarewave voltammetry (SWV) of 3 mM **2**, 2 mM **3**, 2 mM **11**, 3 mM **15**, and 3 mM **16** obtained by a Pt electrode vs. Ag/Ag⁺ using 0.1 M of tetrabutylammonium tetrafluoroborate in ACN.

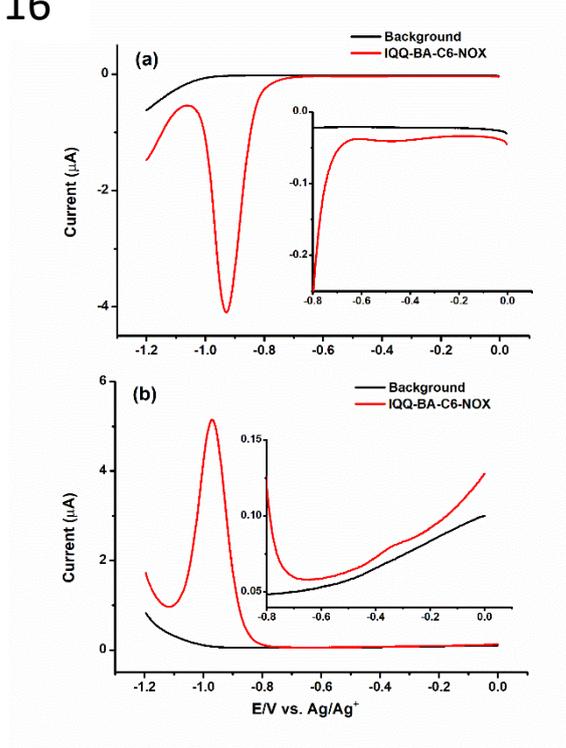


11



15

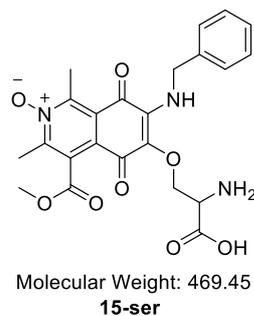
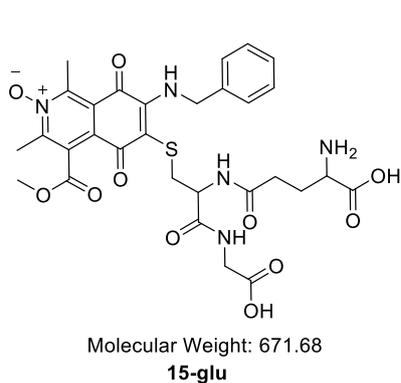
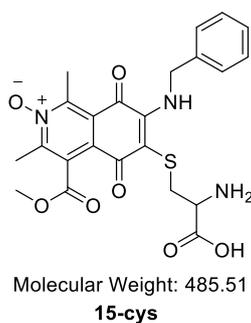
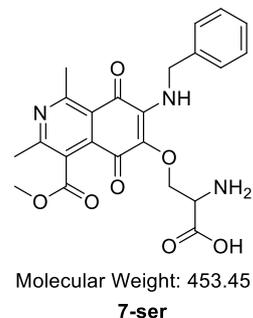
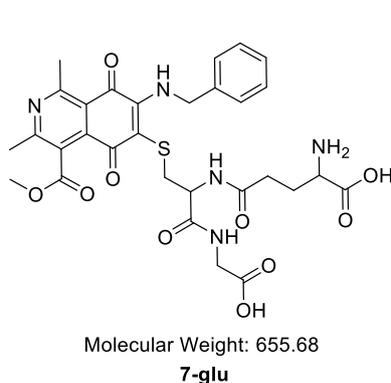
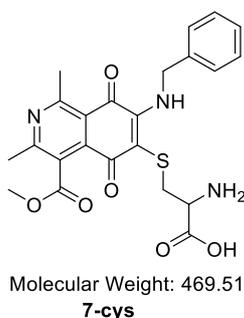
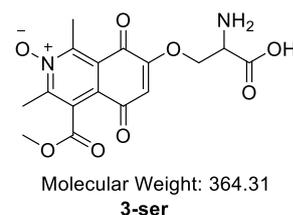
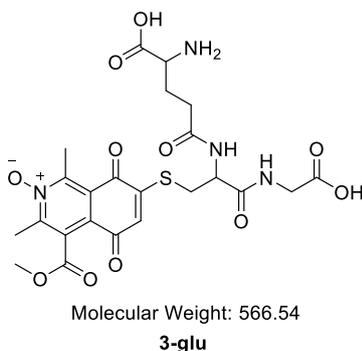
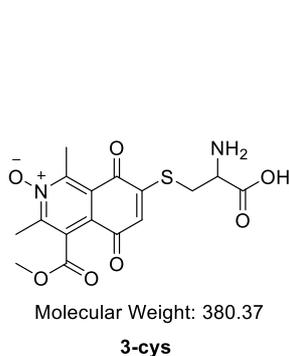
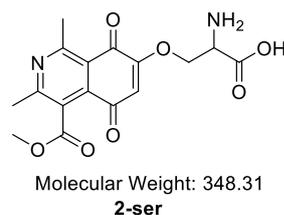
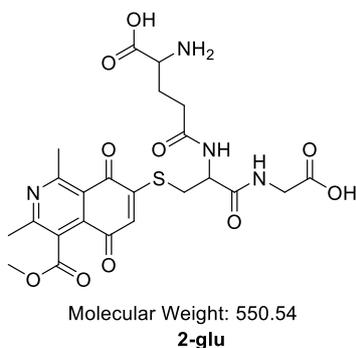
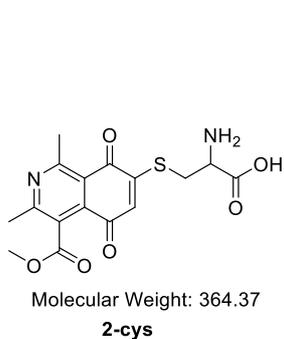




Adduct Binding Studies

Predicted adducts

Compounds **2**, **3**, **7** and **15** proposed adducts are shown. Compound **11** adducts are identical to compound **7** adducts due to loss of bromine. Compound **16** is opposite isomer to compound **15**, thus mass of adducts formed would be identical.



LC/MS procedure and information

LC/MS : Acquity BSM, Acquity Sample Manager, Vion IMS QTof (SAA055K)

Column: Acquity UPLC-BEH-C18

Column Dimension : 2.1 mm x 50 mm

Column Particle Size : 1.7 μ m

Mode: ESI⁺

Mobile Phase: See Below

Gradient: See Below

Flow Rate: 0.600 mL/min

Sample Run Time: 5 minutes

Injection Volume: 1 μ L with a 2 μ L dilution

Mobile Phases and Gradients

Solvent A = Water + 0.1% Formic Acid

Solvent B = Acetonitrile + 0.1 % Formic Acid

Time (min)	Composition A (%)	Composition B (%)	Curve
0.00	98.0	2.0	Initial
0.50	98.0	2.0	6
2.00	50.0	50.0	6
4.00	5.0	95.0	6
4.10	98.0	2.0	6
5.00	98.0	2.0	6

Vion IMS QTof Source Parameters

Desolvation temperature:	450 °C	Cone gas:	50 L/hr
Desolvation gas:	800 L/hr	Capillary Voltage:	1.00 kV
Source Temperature:	120 °C	Scan Time:	0.200 s

LC/MS Results

Entry	Biological Nucleophile	Retention Time	Observed mass [m/z, (M+H ⁺)]	Detector Response
2	Cysteine	1.3	365.0798	20,237
	Glutathione	1.18	551.1445	10,072
	Serine	1.6	349.1026	20,342
3	Cysteine	1.39	381.0750	11,416
	Glutathione	1.14	567.1396	4154
	Serine	1.41	365.0981	1,017
7	Cysteine	1.88	470.1385	516
	Glutathione	1.83	656.2014	737
	Serine	N/A	N/A	N/A
11	Cysteine	1.88	470.1376	1,742
	Glutathione	1.83	656.2030	3,856
	Serine	N/A	N/A	N/A
15	Cysteine	1.72	486.1328	3,893
	Glutathione	1.68	672.1991	4,324
	Serine	N/A	N/A	N/A
16	Cysteine	1.78	486.1348	208
	Glutathione	1.76	672.1984	4,713
	Serine	N/A	N/A	N/A