FIG. 1A

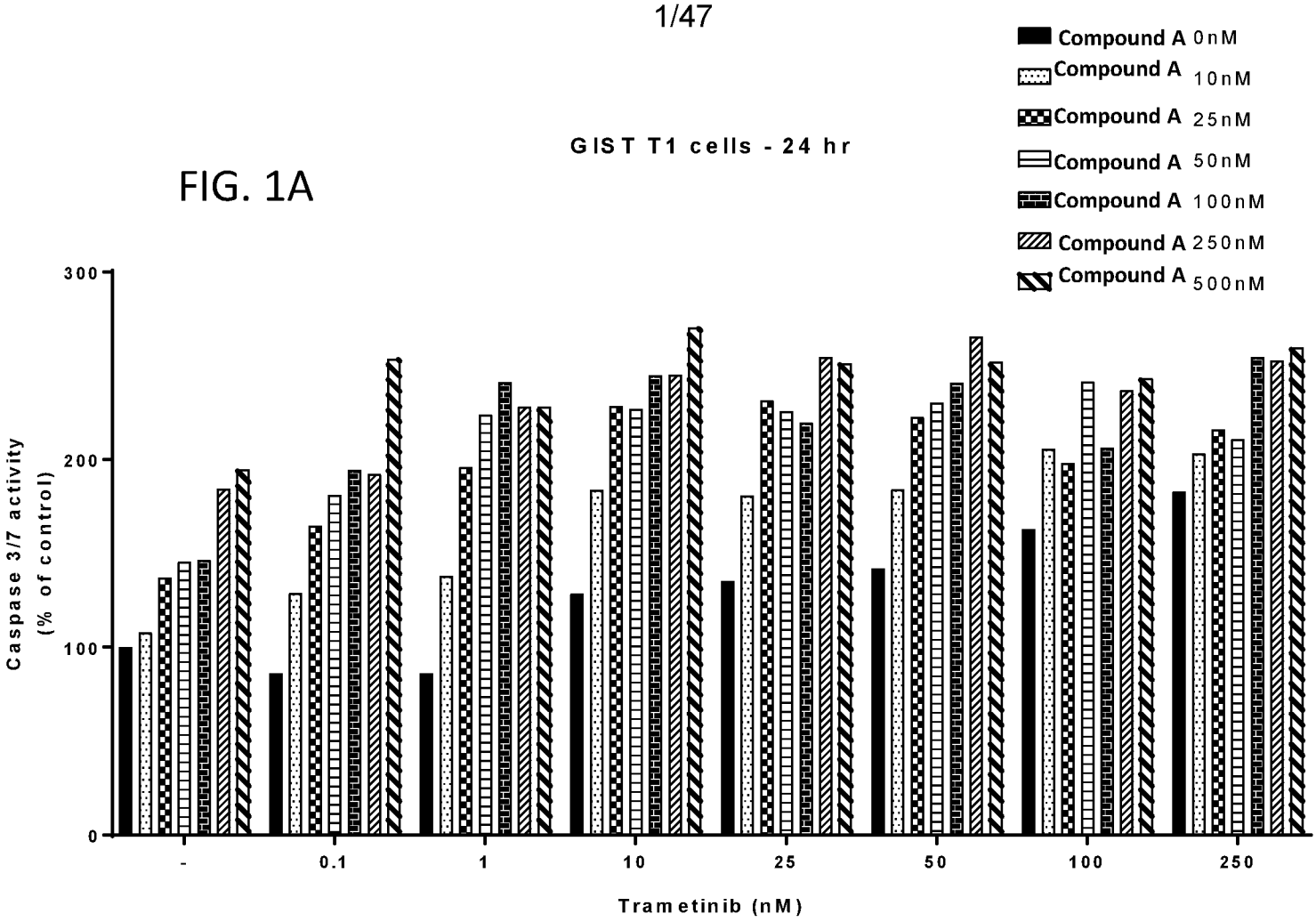


FIG. 1B

Combination index by Chou Talalay analysis

CI<1 = synergy
CI=1 = additive effect
CI>1 = antagonism

CI	Compound A 10nM	Compound A 25nM	Compound A 50nM	Compound A 100nM	Compound A 250nM	Compound A 500nM
Trametinib 0.1nM	0.41635	0.20181	0.18684	0.19377	0.53669	0.01446
Trametinib 1nM	0.32337	0.04483	0.01746	0.00975	0.06517	0.13033
Trametinib 10nM	0.04689	0.00672	0.01463	0.00706	0.01761	0.0012
Trametinib 25nM	0.08445	0.00557	0.01592	0.0473	0.00679	0.01911
Trametinib 50nM	0.1024	0.01154	0.01213	0.01019	0.00149	0.01747
Trametinib 100nM	0.03211	0.0835	0.00501	0.12226	0.03448	0.0413
Trametinib 250nM	0.07868	0.03424	0.07228	0.00273	0.00836	0.007

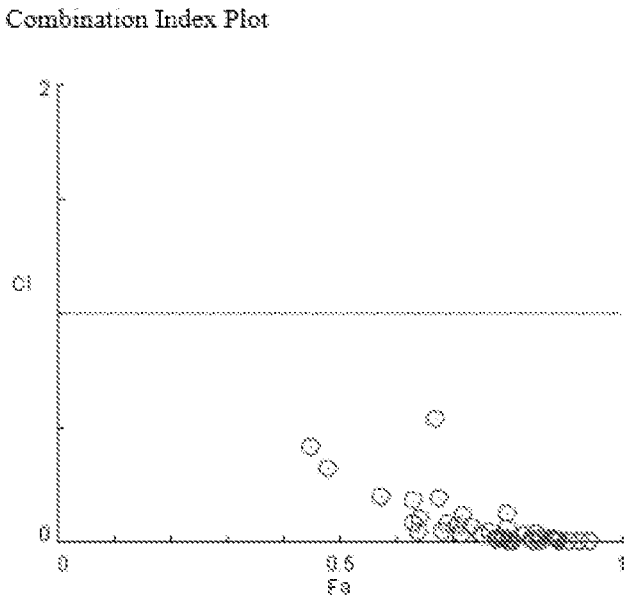


FIG. 1C

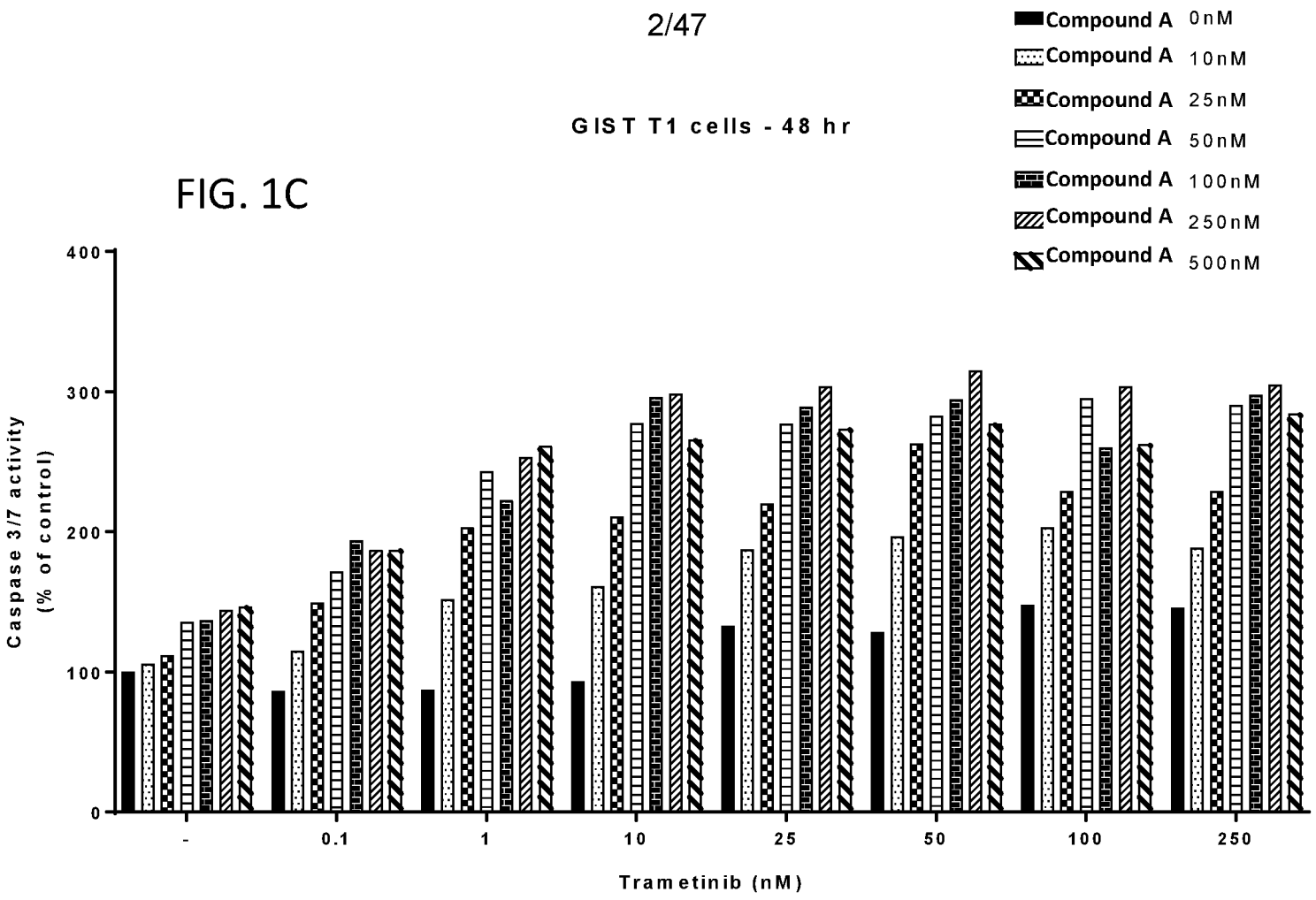


FIG. 1D **Combination index by Chou Talalay analysis**

CI	Compound A 10nM	Compound A 25nM	Compound A 50nM	Compound A 100nM	Compound A 250nM	Compound A 500nM
Trametinib 0.1nM	0.544	0.06109	0.01804	0.00494	0.02246	0.04491
Trametinib 1nM	0.02154	5.23E-04	1.55E-05	3.09E-04	2.10E-05	1.29E-05
Trametinib 10nM	0.01666	2.97E-04	7.82E-08	9.90E-10	9.00E-10	6.44E-06
Trametinib 25nM	0.0022	1.33E-04	8.55E-08	9.57E-09	5.70E-11	1.63E-06
Trametinib 50nM	0.00133	6.05E-07	2.55E-08	1.79E-09	1.10E-21	8.28E-07
Trametinib 100nM	0.00116	8.38E-05	7.50E-10	3.55E-06	5.70E-11	1.09E-05
Trametinib 250nM	0.01223	1.51E-04	4.04E-09	5.00E-10	3.10E-11	1.69E-07

CI<1 = synergy
CI=1 = additive effect
CI>1 = antagonism

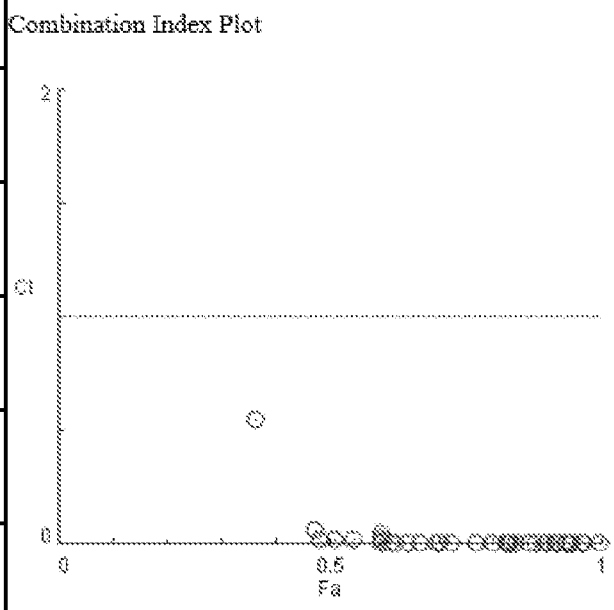


FIG. 1E

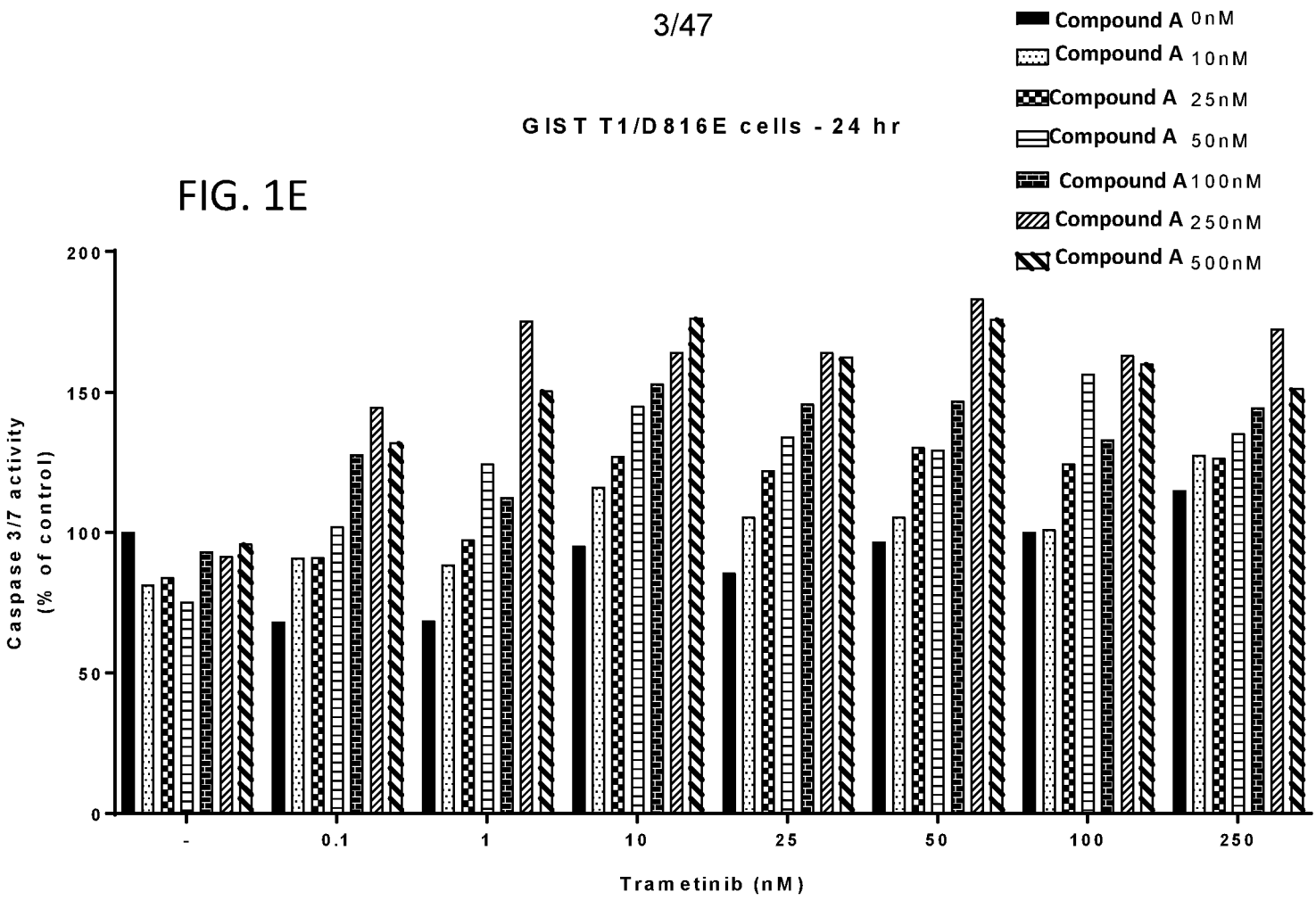


FIG. 1F

Combination index by Chou Talalay analysis

CI index	Compound A 10nM	Compound A 25nM	Compound A 50nM	Compound A 100nM	Compound A 250nM	Compound A 500nM
Trametinib 0.1nM	0.05427	0.11928	0.0195	0.000143	8.28E-06	0.000253
Trametinib 1nM	0.18113	0.0469	0.02853	0.00535	7.11E-08	8.34E-06
Trametinib 10nM	0.01105	0.00199	0.000117	3.21E-05	5.07E-06	5.61E-07
Trametinib 25nM	0.14462	0.01078	0.00166	0.000258	1.26E-05	1.64E-05
Trametinib 50nM	0.28757	0.00592	0.00668	0.000438	7.57E-07	2.91E-06
Trametinib 100nM	1.18272	0.02898	0.000185	0.00772	5.94E-05	9.92E-05
Trametinib 250nM	0.04532	0.05299	0.01351	0.00313	0.000029	0.00106

CI<1 = synergy
CI=1 = additive effect
CI>1 = antagonism

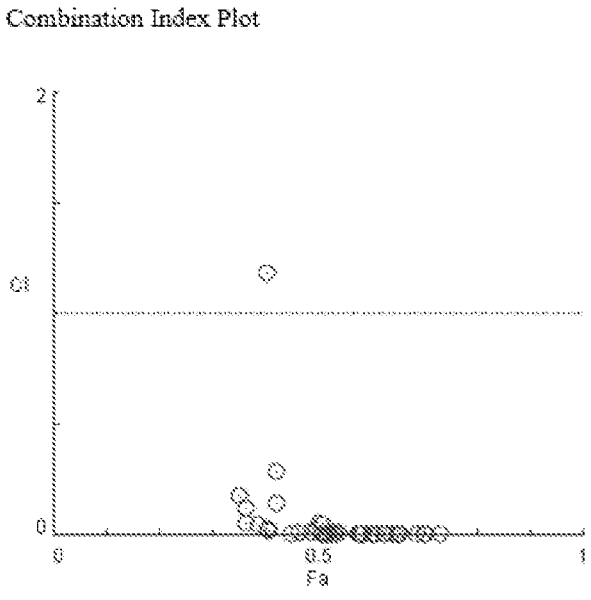


FIG. 1G

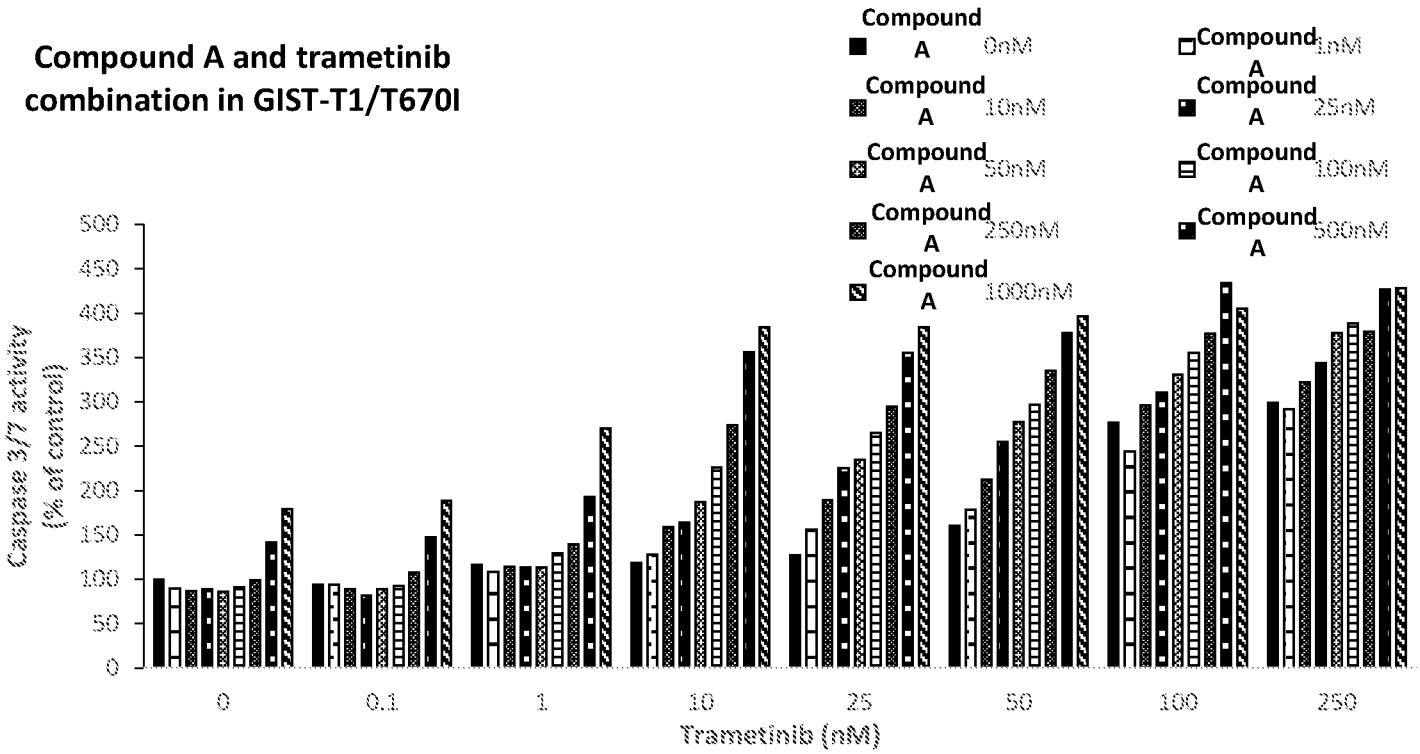


FIG. 1H **Combination index by Chou Talalay analysis**

CI	Compound A 10nM	Compound A 25nM	Compound A 50nM	Compound A 100nM	Compound A 250nM	Compound A 500nM	Compound A 1000nM
Trametinib 1 nM	0.89607	1.05715	1.20054	0.54408	0.42371	0.03244	0.00155
Trametinib 10 nM	1.04701	0.8501	0.32966	0.07514	0.0131	5.13E-04	1.32E-04
Trametinib 25 nM	0.74569	0.19466	0.13966	0.04476	0.01521	0.00128	3.14E-04
Trametinib 50 nM	0.63181	0.12923	0.05747	0.02767	0.00618	8.94E-04	3.39E-04
Trametinib 100 nM	0.0564	0.03232	0.01456	0.00513	0.00183	5.78E-05	4.17E-04
Trametinib 250 nM	0.05133	0.02117	0.00447	0.00255	0.00425	2.46E-04	2.20E-04

CI<1 = synergy
CI=1 = additive effect
CI>1 = antagonism

Combination Index Plot

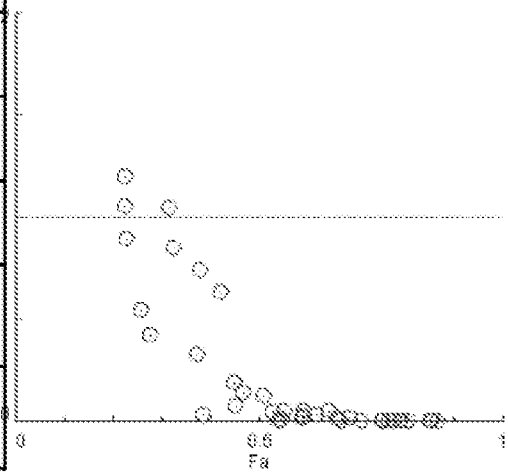


FIG. 2A

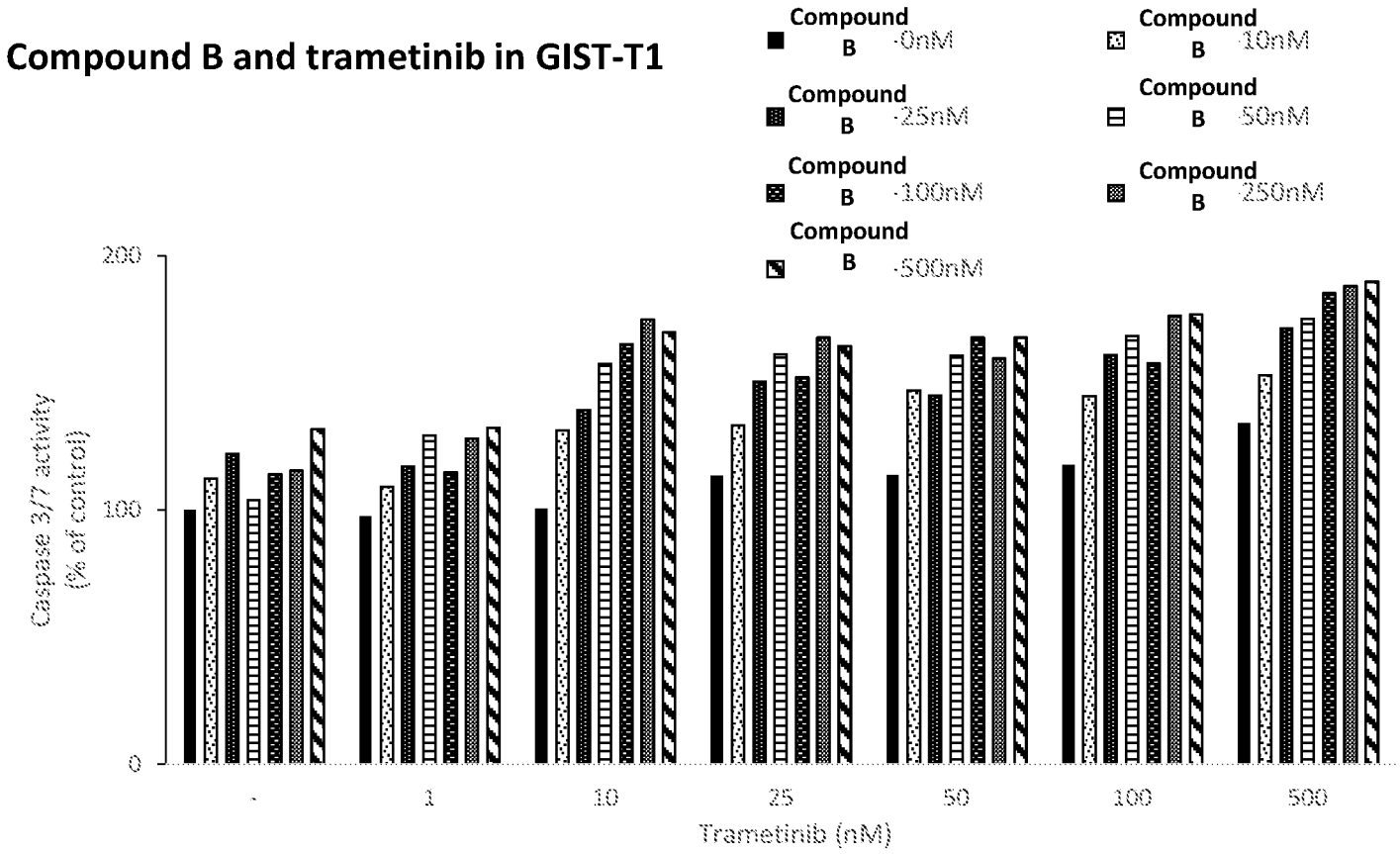


FIG. 2B

Combination index by Chou Talalay analysis

CI Index	Compound B 10nM	Compound B 25nM	Compound B 50nM	Compound B 100nM	Compound B 250nM	Compound B 500nM
Trametinib 1nm	1.39845	0.30024	0.01632	2.30138	0.10126	0.064
Trametinib 10nm	0.02443	0.00825	6.55E-04	2.14E-04	4.87E-05	1.10E-04
Trametinib 25nm	0.04489	0.00449	9.92E-04	0.00355	3.69E-04	5.99E-04
Trametinib 50nm	0.014	0.0184	0.00206	7.38E-04	0.00246	7.39E-04
Trametinib 100nm	0.03929	0.00411	0.00137	0.00631	4.00E-04	3.70E-04
Trametinib 500nm	0.06136	0.00435	0.00244	4.54E-04	2.94E-04	2.15E-04

CI<1 = synergy
CI=1 = additive effect
CI>1 = antagonism

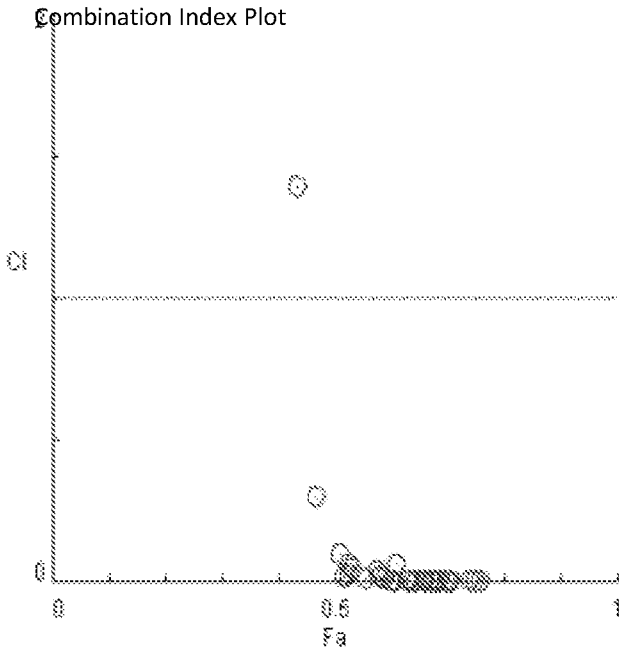


FIG. 2C

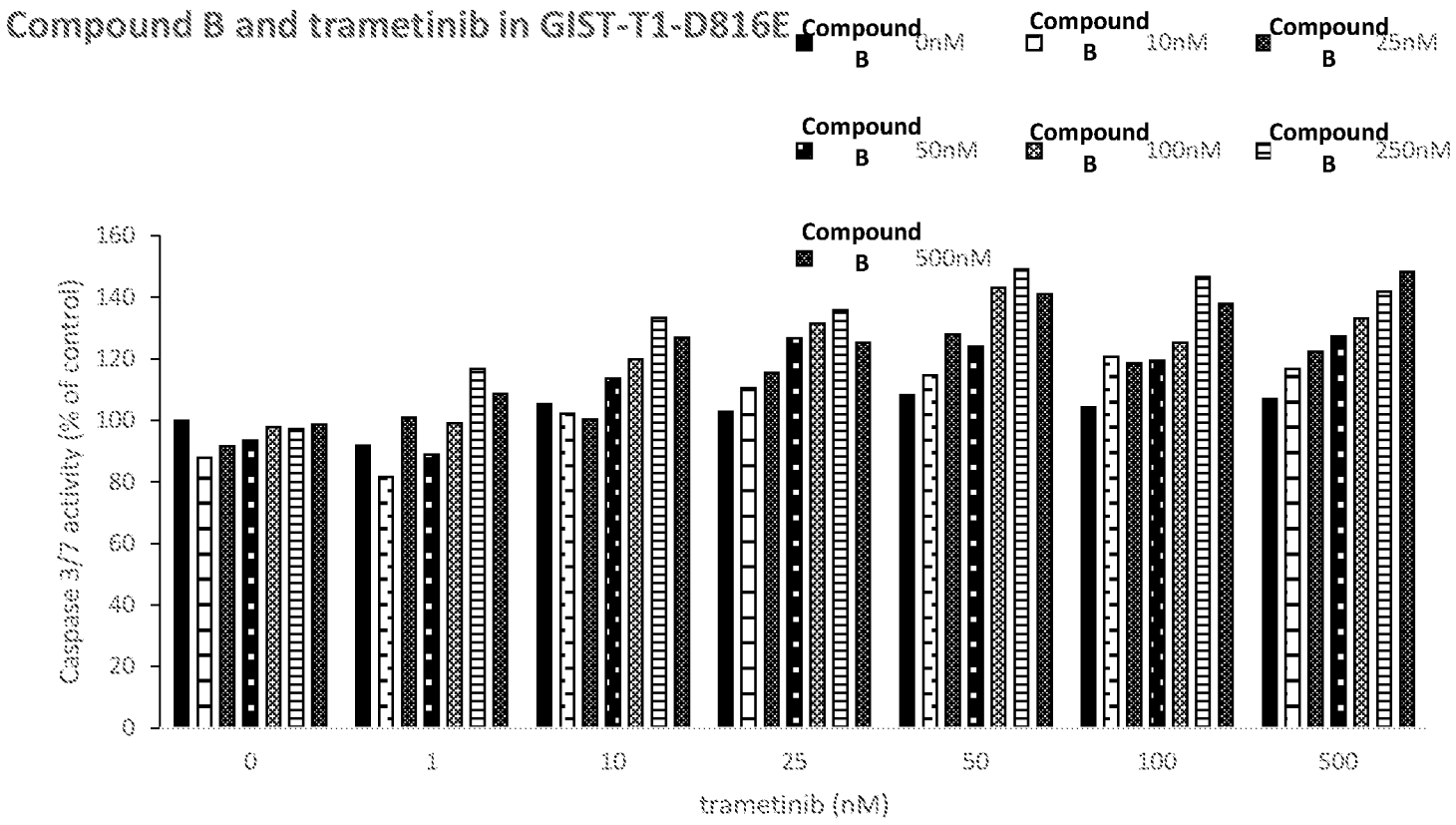


FIG. 2D **Combination index by Chou Talalay analysis**

CI<1 = synergy
CI=1 = additive effect
CI>1 = antagonism

CI	Compound B 10nM	Compound B 25nM	Compound B 50nM	Compound B 100nM	Compound B 250nM	Compound B 500nM
Trametinib 1 nM	665.864	0.12785	26.2251	0.45772	0.00161	0.04969
Trametinib 10 nM	0.54776	1.20639	0.00454	4.57E-04	6.01E-06	1.07E-04
Trametinib 25 nM	0.03782	0.0046	4.67E-05	8.93E-06	2.92E-06	2.39E-04
Trametinib 50 nM	0.01217	4.63E-05	2.61E-04	1.36E-07	2.74E-08	9.66E-07
Trametinib 100 nM	0.00188	0.00445	0.0033	3.10E-04	8.20E-08	3.44E-06
Trametinib 500 nM	0.04614	0.00446	5.99E-04	4.82E-05	1.36E-06	1.23E-07

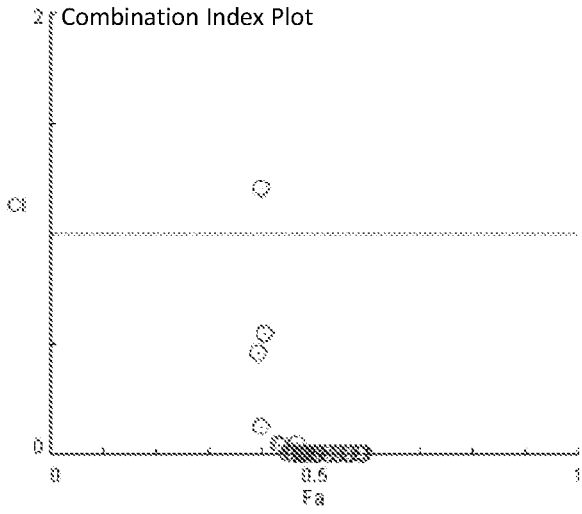


FIG. 2E

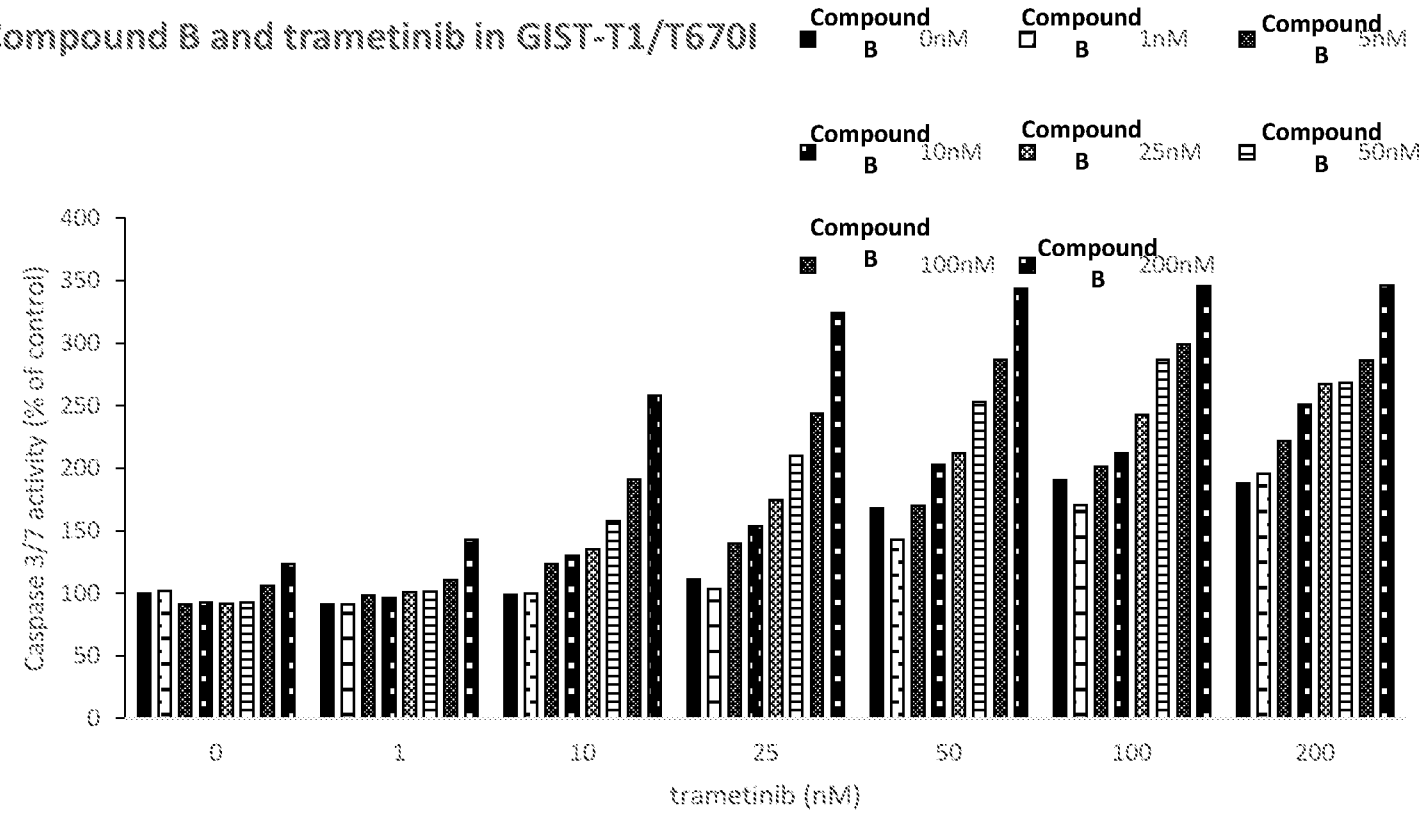


FIG. 2F

Combination index by Chou Talalay analysis

CI<1 = synergy
CI=1 = additive effect
CI>1 = antagonism

CI	Compound B 1nM	Compound B 5nM	Compound B 10nM	Compound B 25nM	Compound B 50nM	Compound B 100nM	Compound B 200nM
Trametinib 1 nM	1.14152	0.68225	1.61409	0.98075	1.71864	0.29552	0.03118
Trametinib 10 nM	2.69122	0.75205	0.55106	0.43683	0.16308	0.04278	0.0037
Trametinib 25 nM	5.2964	0.89005	0.48271	0.20367	0.05226	0.01535	7.67E-04
Trametinib 50 nM	1.55676	0.48782	0.13831	0.09887	0.02177	0.00642	6.93E-04
Trametinib 100 nM	0.95619	0.29266	0.19773	0.06368	0.01283	0.00935	0.00127
Trametinib 200 nM	0.72063	0.27355	0.09362	0.05242	0.04964	0.02614	0.0108

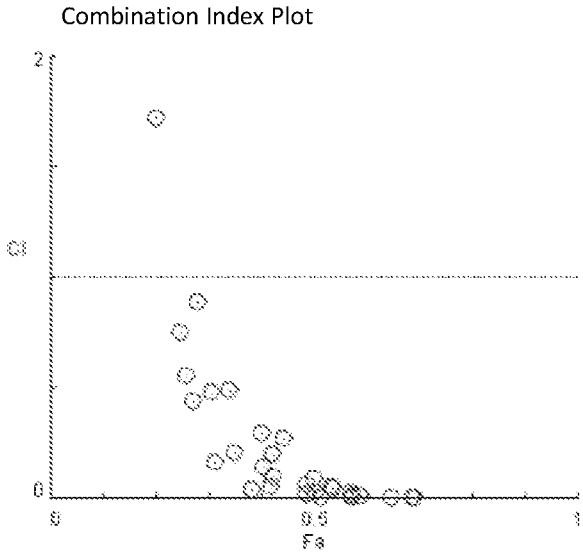


FIG. 3A

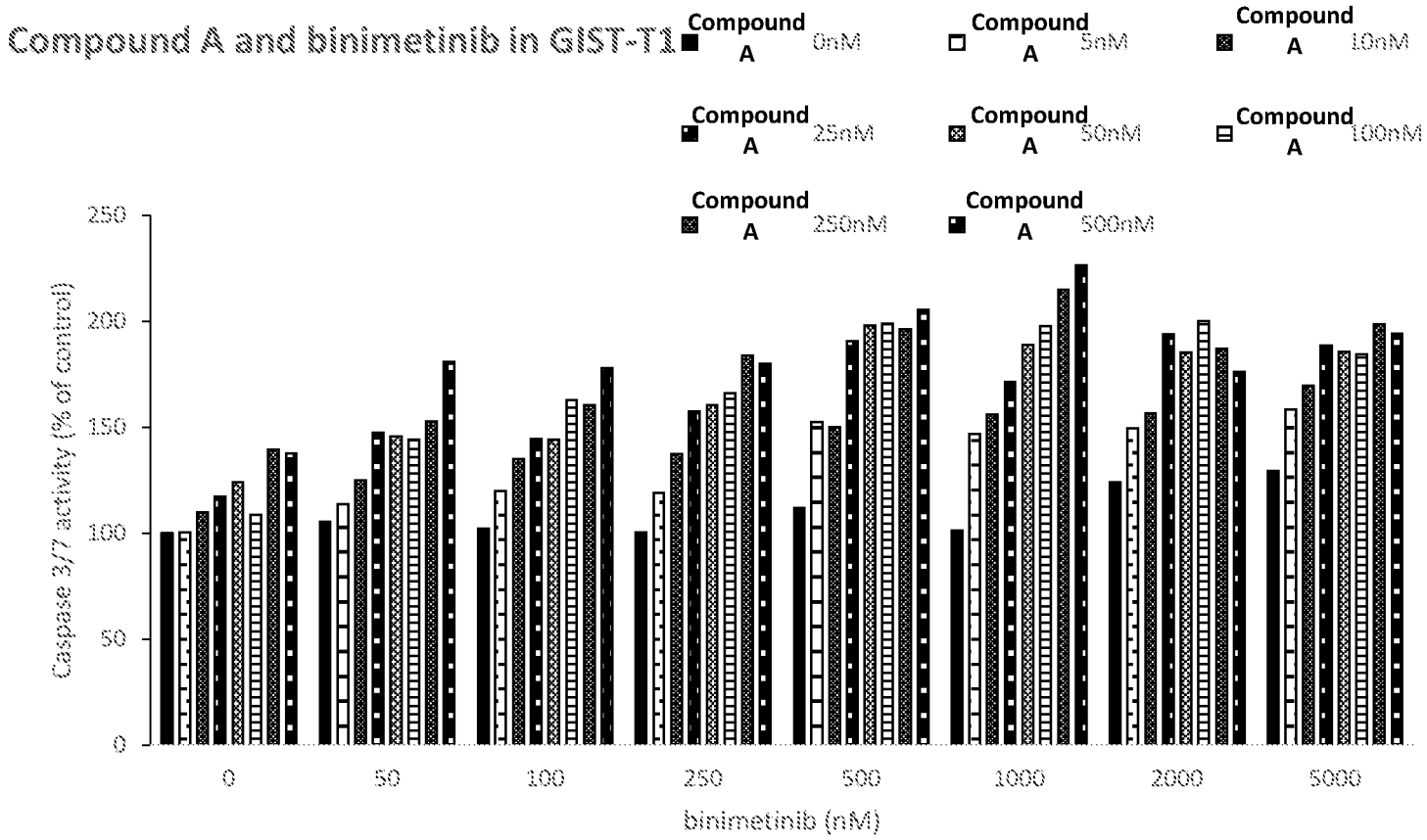


FIG. 3B **Combination index by Chou Talalay analysis**

CI<1 = synergy
CI=1 = additive effect
CI>1 = antagonism

CI	Compound A 0nM	Compound A 5nM	Compound A 10nM	Compound A 25nM	Compound A 50nM	Compound A 100nM	Compound A 250nM
Binimetinib 50 nM	0.33162	0.11367	0.01361	0.03539	0.08336	0.05317	0.0021
Binimetinib 100 nM	0.13977	0.03047	0.02054	0.04202	0.00686	0.0182	0.00352
Binimetinib 250 nM	0.2221	0.00601	0.00355	0.0046	0.00416	5.34E-04	0.00246
Binimetinib 500 nM	0.00186	0.00463	2.11E-05	1.03E-05	1.45E-05	5.78E-05	2.16E-05
Binimetinib 1000 nM	0.00584	0.0022	4.83E-04	5.74E-05	2.16E-05	9.19E-07	5.62E-08
Binimetinib 2000 nM	0.00526	0.00249	1.18E-05	1.11E-04	1.39E-05	3.10E-04	0.00447
Binimetinib 5000 nM	0.00224	4.19E-04	3.22E-05	1.09E-04	2.53E-04	3.75E-05	2.22E-04

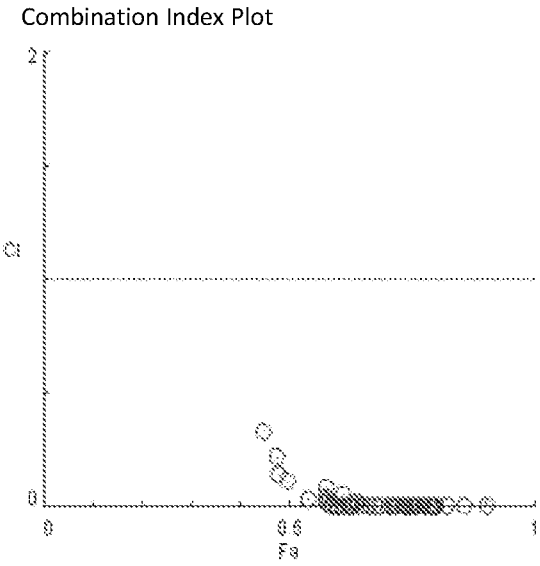


FIG. 3C

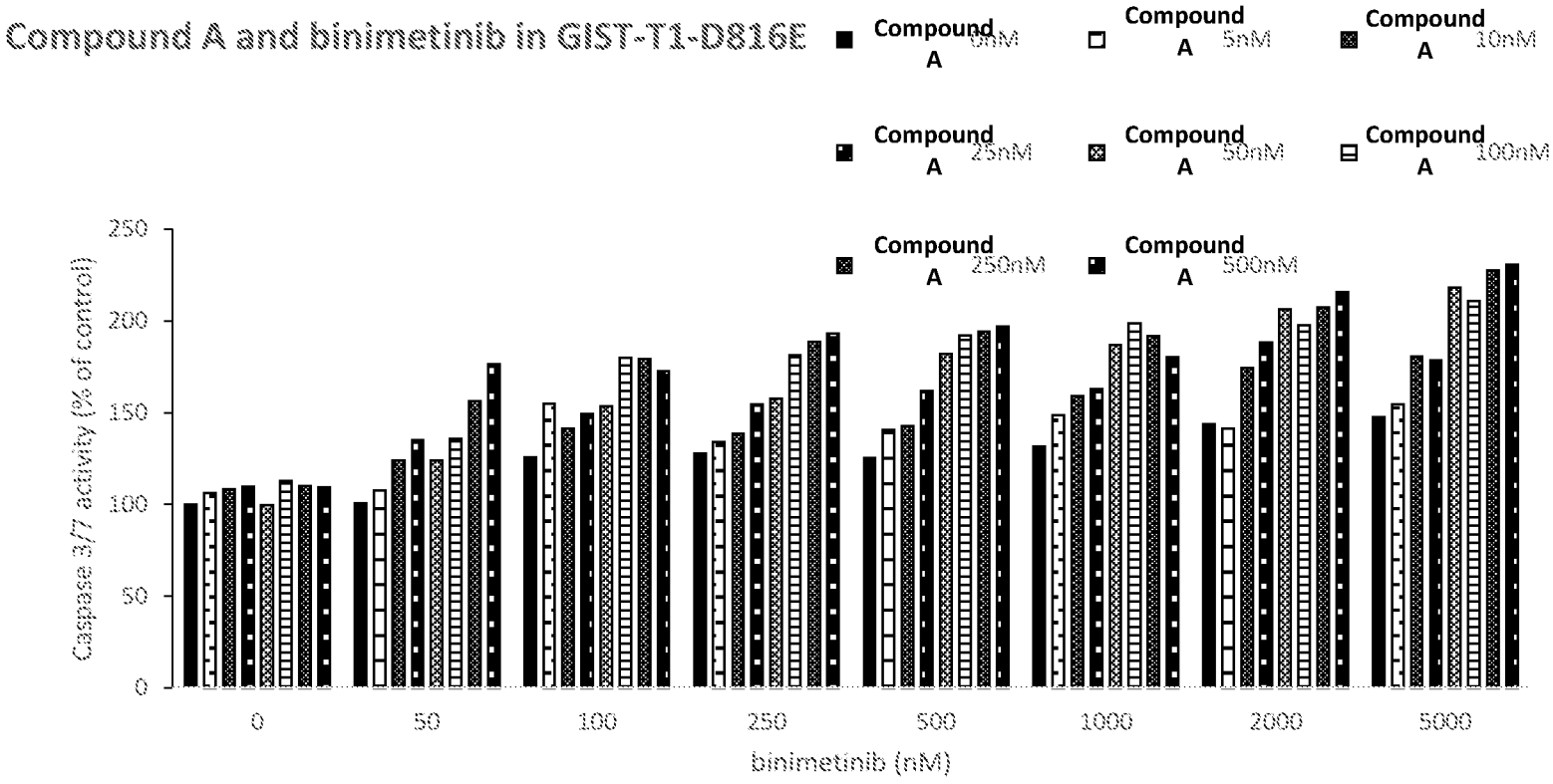


FIG. 3D **Combination index by Chou Talalay analysis**

CI<1 = synergy
CI=1 = additive effect
CI>1 = antagonism

CI	Compound A 5nM	Compound A 10nM	Compound A 25nM	Compound A 50nM	Compound A 100nM	Compound A 250nM	Compound A 500nM
Binimetinib 50 nM	1.44226	0.18041	0.04953	0.18041	0.04533	0.00368	2.70E-04
Binimetinib 100 nM	0.00887	0.04581	0.018	0.01068	3.28E-04	3.65E-04	9.10E-04
Binimetinib 250 nM	0.27864	0.16365	0.02359	0.01571	6.58E-04	2.18E-04	1.05E-04
Binimetinib 500 nM	0.25046	0.19724	0.0189	0.00118	2.38E-04	1.70E-04	1.06E-04
Binimetinib 1000 nM	0.19128	0.05539	0.03323	0.0011	1.63E-04	5.17E-04	0.00294
Binimetinib 2000 nM	0.91612	0.0148	0.00181	7.43E-05	3.72E-04	5.74E-05	8.87E-06
Binimetinib 5000 nM	0.4718	0.01468	0.01892	1.25E-05	7.15E-05	6.91E-07	2.20E-07

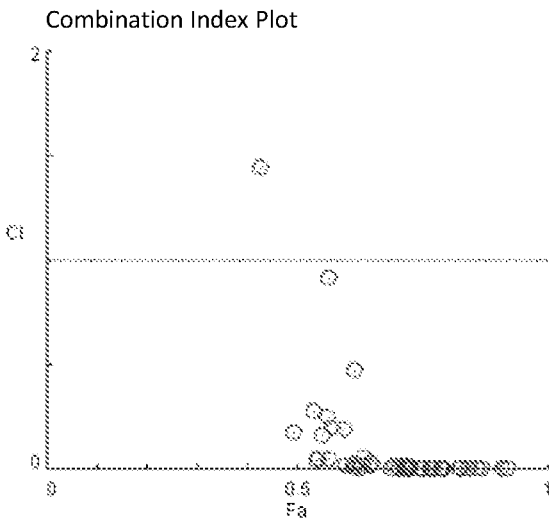


FIG. 3E

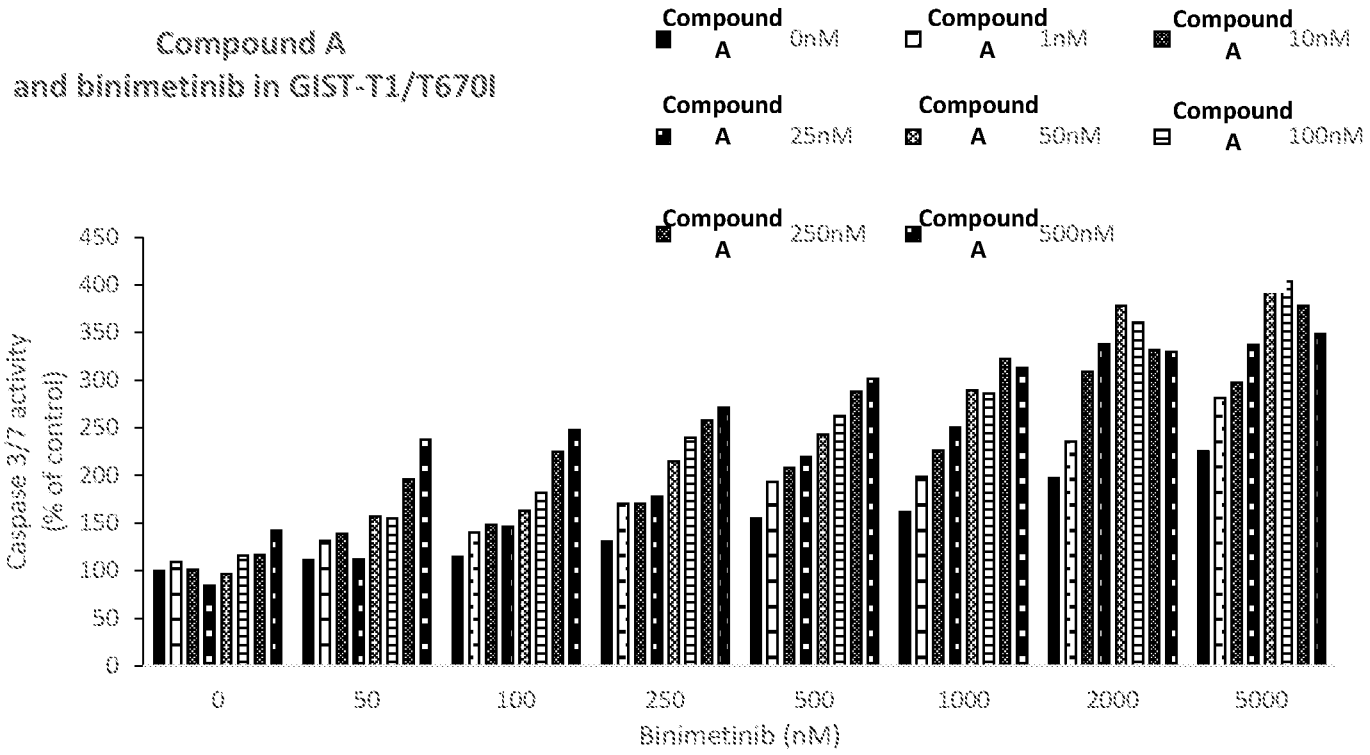


FIG. 3F **Combination index by Chou Talalay analysis**

CI<1 = synergy
CI=1 = additive effect
CI>1 = antagonism

CI	Compound A 5nM	Compound A 10nM	Compound A 25nM	Compound A 50nM	Compound A 100nM	Compound A 250nM	Compound A 500nM
Binimetinib 50 nM	0.26759	0.19769	0.97922	0.09229	0.1009	0.02216	0.00492
Binimetinib 100 nM	0.37303	0.26335	0.28329	0.31079	0.07363	0.01588	0.00691
Binimetinib 250 nM	0.27979	0.27979	0.21379	0.05549	0.02307	0.0121	0.00751
Binimetinib 500 nM	0.2403	0.14108	0.0946	0.04058	0.02056	0.00922	0.00547
Binimetinib 1000 nM	0.40206	0.1466	0.06912	0.01474	0.01722	0.00394	0.00588
Binimetinib 2000 nM	0.21654	0.01366	0.00386	4.15E-04	0.0012	0.00506	0.00572
Binimetinib 5000 nM	0.10041	0.05372	0.01007	3.42E-04	1.38E-04	0.00104	0.00569

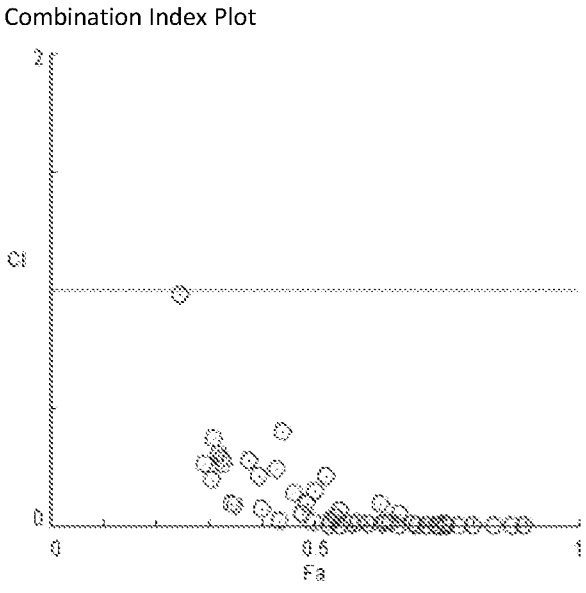
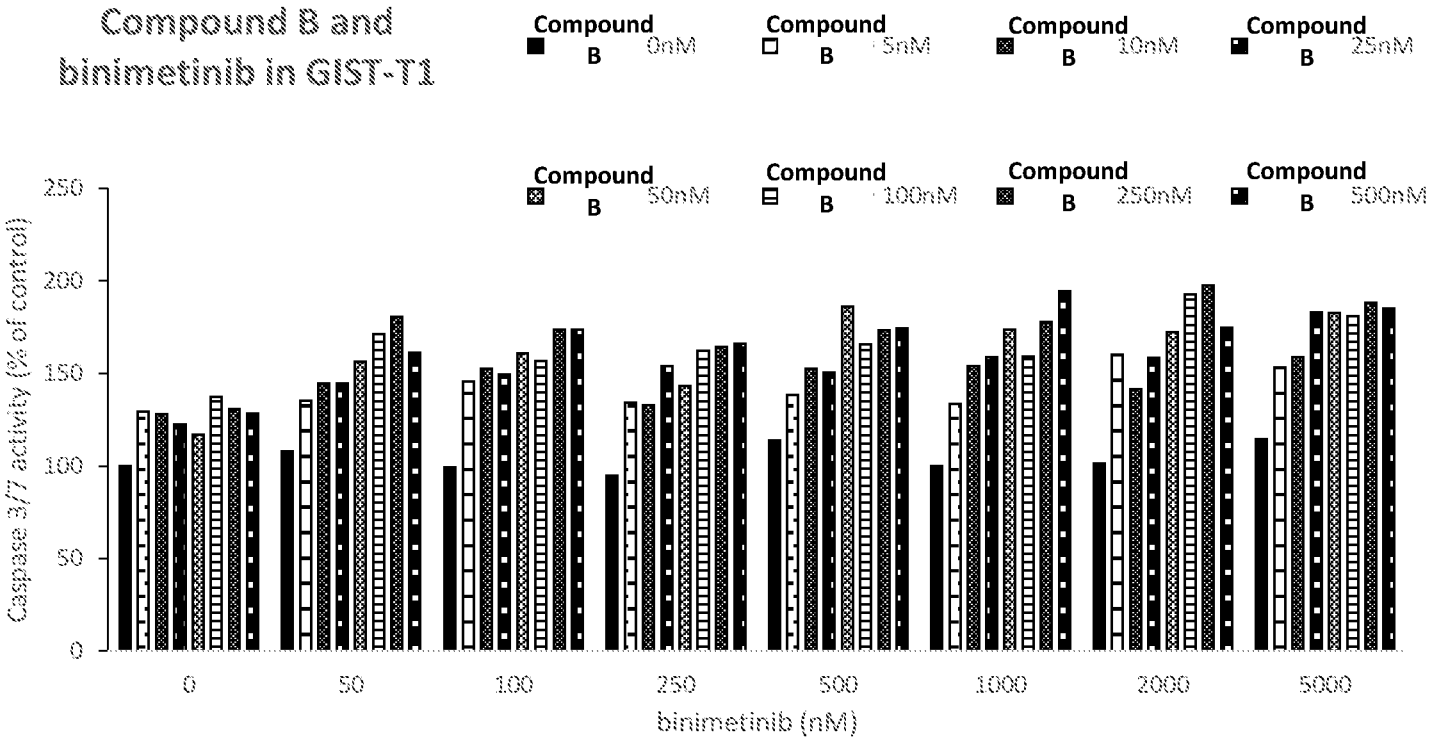


FIG. 4A



Combination index by Chou Talalay analysis

CI<1 = synergy
CI=1 = additive effect
CI>1 = antagonism

FIG. 4B

CI	Compound B 5nM	Compound B 10nM	Compound B 25nM	Compound B 50nM	Compound B 100nM	Compound B 250nM	Compound B 500nM
Binimetinib 50 nM	4.65E-06	1.70E-11	3.20E-11	4.90E-19	7.80E-28	2.00E-34	5.50E-22
Binimetinib 100 nM	1.40E-12	4.60E-17	1.40E-14	1.10E-21	3.70E-19	4.30E-29	5.80E-29
Binimetinib 250 nM	1.39E-05	1.87E-04	1.80E-17	3.80E-10	4.30E-22	4.00E-23	5.50E-24
Binimetinib 500 nM	4.02E-08	5.20E-17	2.20E-17	4.50E-39	1.40E-23	4.00E-28	8.40E-29
Binimetinib 1000 nM	4.15E-05	1.80E-17	7.80E-20	5.80E-28	6.50E-20	3.80E-31	4.10E-54
Binimetinib 2000 nM	5.10E-20	1.44E-09	3.00E-19	7.20E-27	3.00E-49	7.20E-68	1.80E-28
Binimetinib 5000 nM	1.30E-16	4.80E-19	4.90E-35	1.20E-34	5.80E-33	7.00E-41	3.70E-37

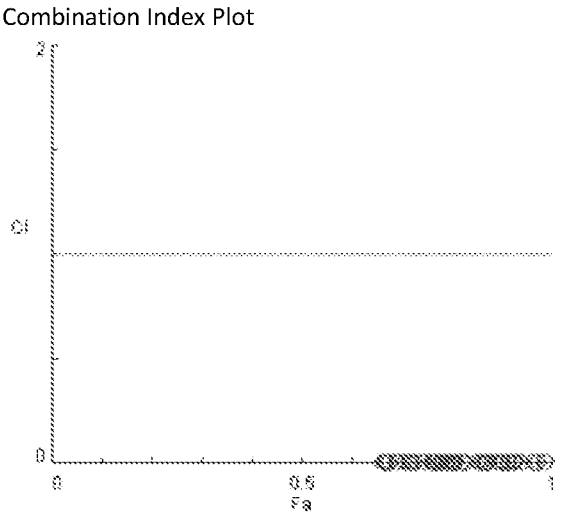


FIG. 4C

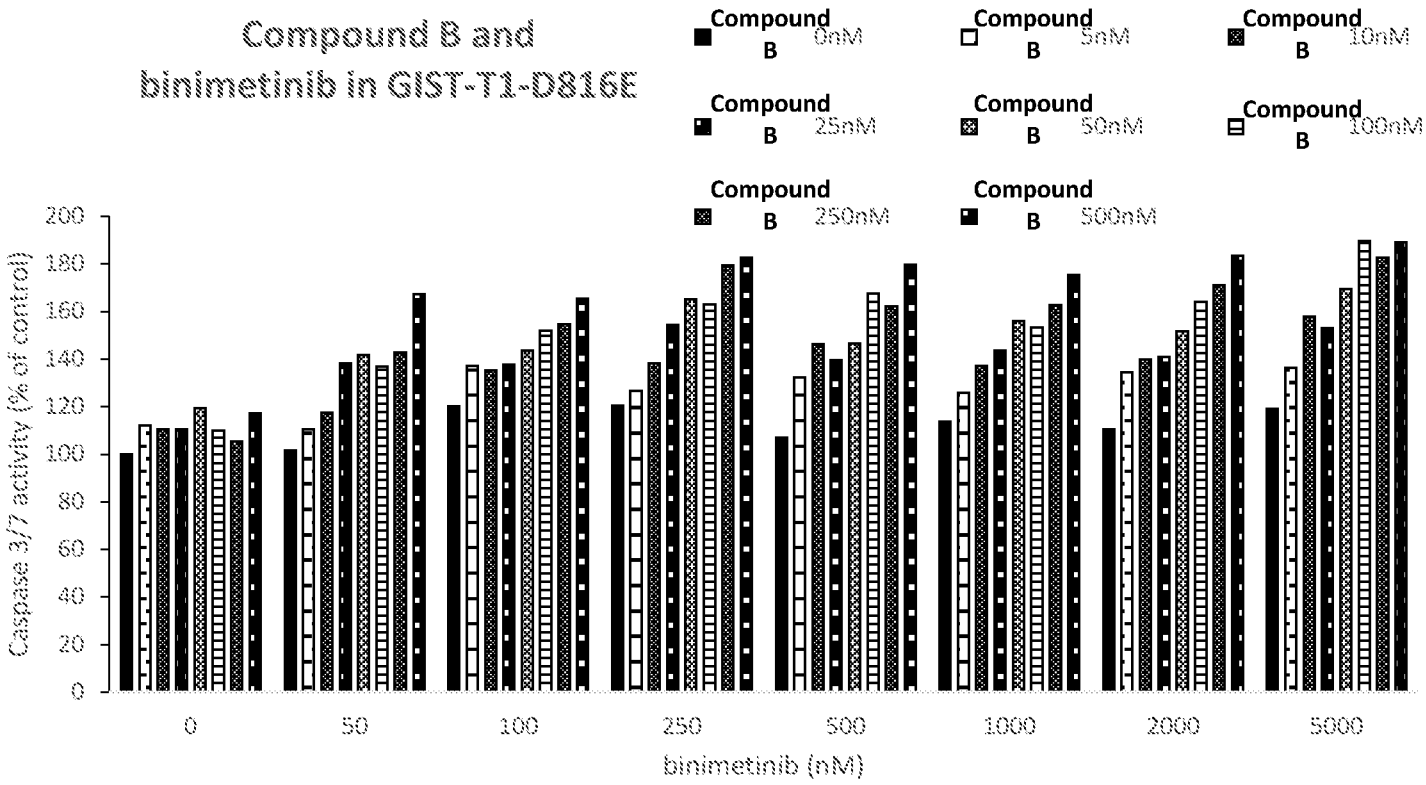


FIG. 4D **Combination index by Chou Talalay analysis**

CI<1 = synergy
CI=1 = additive effect
CI>1 = antagonism

CI	Compound B 5nM	Compound B 10nM	Compound B 25nM	Compound B 50nM	Compound B 100nM	Compound B 250nM	Compound B 500nM
Binimetinib 50 nM	1606.78	0.00356	9.50E-11	3.40E-12	3.40E-10	1.10E-12	9.80E-25
Binimetinib 100 nM	4.70E-10	2.81E-09	2.70E-10	1.20E-12	2.60E-16	1.60E-17	3.10E-23
Binimetinib 250 nM	9.63E-06	4.80E-10	3.90E-17	1.00E-22	1.80E-21	6.80E-33	3.20E-36
Binimetinib 500 nM	1.64E-07	4.10E-13	3.20E-10	3.30E-13	9.80E-24	1.00E-20	5.80E-33
Binimetinib 1000 nM	8.87E-05	4.71E-09	1.20E-11	3.30E-17	5.90E-16	9.50E-21	6.10E-29
Binimetinib 2000 nM	9.56E-08	8.80E-10	2.90E-10	6.50E-15	4.00E-21	1.40E-25	5.70E-36
Binimetinib 5000 nM	4.83E-08	1.70E-17	4.50E-15	4.00E-24	3.00E-44	6.30E-35	6.30E-43

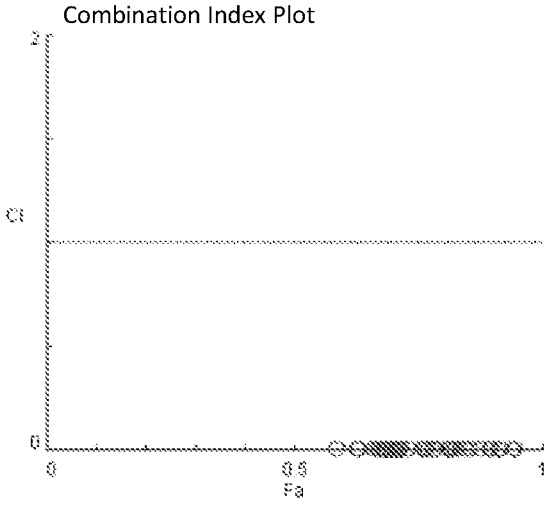


FIG. 4E

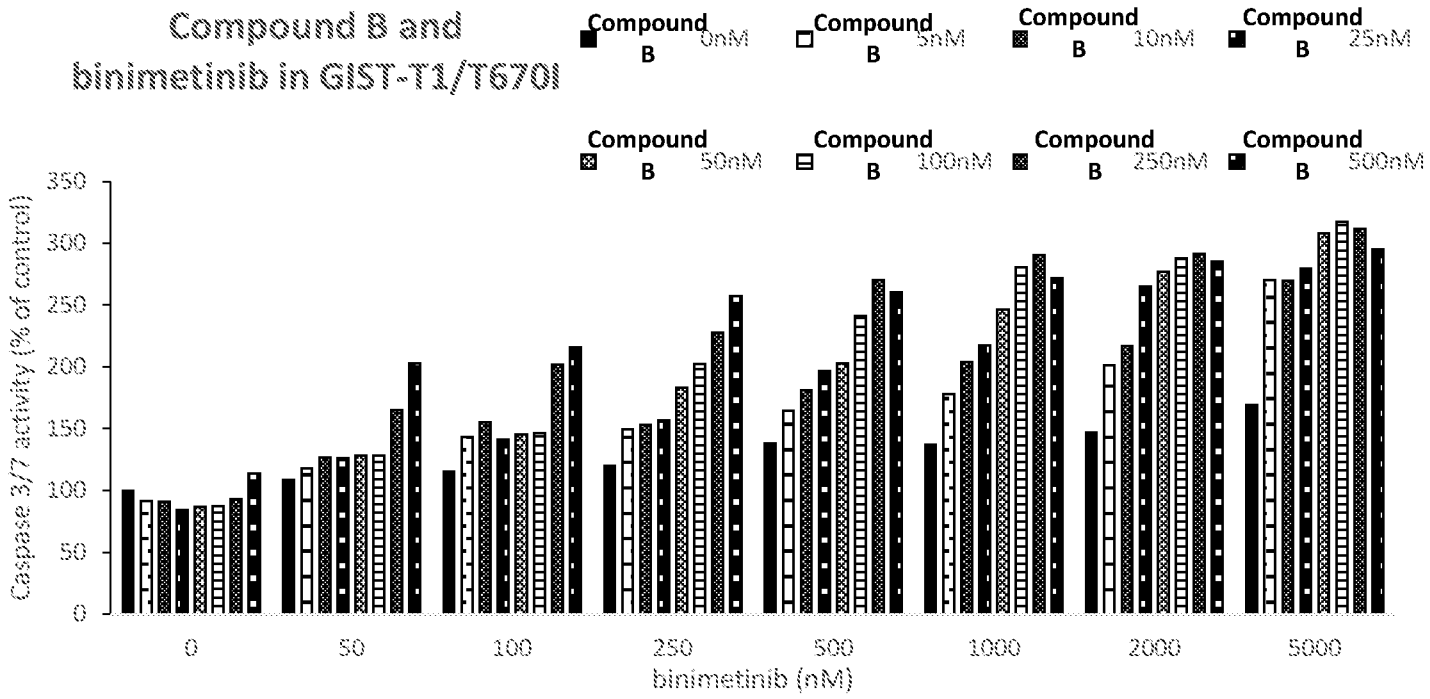


FIG. 4F **Combination index by Chou Talalay analysis**

CI<1 = synergy
CI=1 = additive effect
CI>1 = antagonism

CI	Compound B 5nM	Compound B 10nM	Compound B 25nM	Compound B 50nM	Compound B 100nM	Compound B 250nM	Compound B 500nM
Binimetinib 50 nM	0.34963	0.16862	0.17353	1.08713	0.15037	0.00828	4.63E-04
Binimetinib 100 nM	0.0904	0.03897	0.10661	0.07671	0.06878	0.00101	3.34E-04
Binimetinib 250 nM	0.13837	0.10561	0.07858	0.01969	0.00238	3.25E-04	2.35E-05
Binimetinib 500 nM	0.0897	0.02509	0.00754	0.00476	1.96E-04	1.17E-05	3.46E-05
Binimetinib 1000 nM	0.06371	0.00878	0.00298	2.52E-04	7.39E-06	2.35E-06	2.08E-05
Binimetinib 2000 nM	0.02182	0.00631	8.43E-05	2.32E-05	6.49E-06	3.90E-06	8.47E-06
Binimetinib 5000 nM	1.21E-04	1.26E-04	4.19E-05	7.69E-07	1.09E-07	3.77E-07	5.71E-06

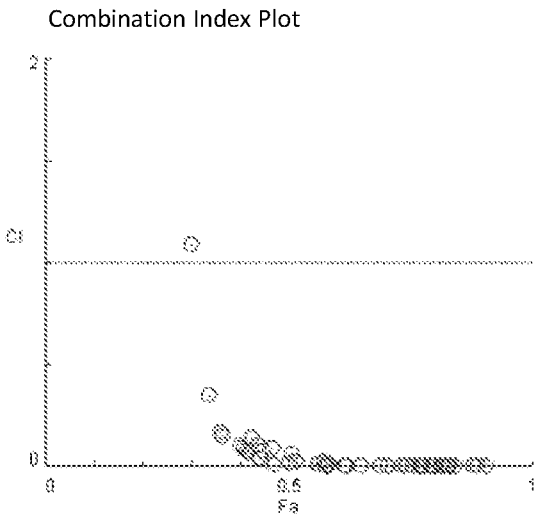


FIG. 5A

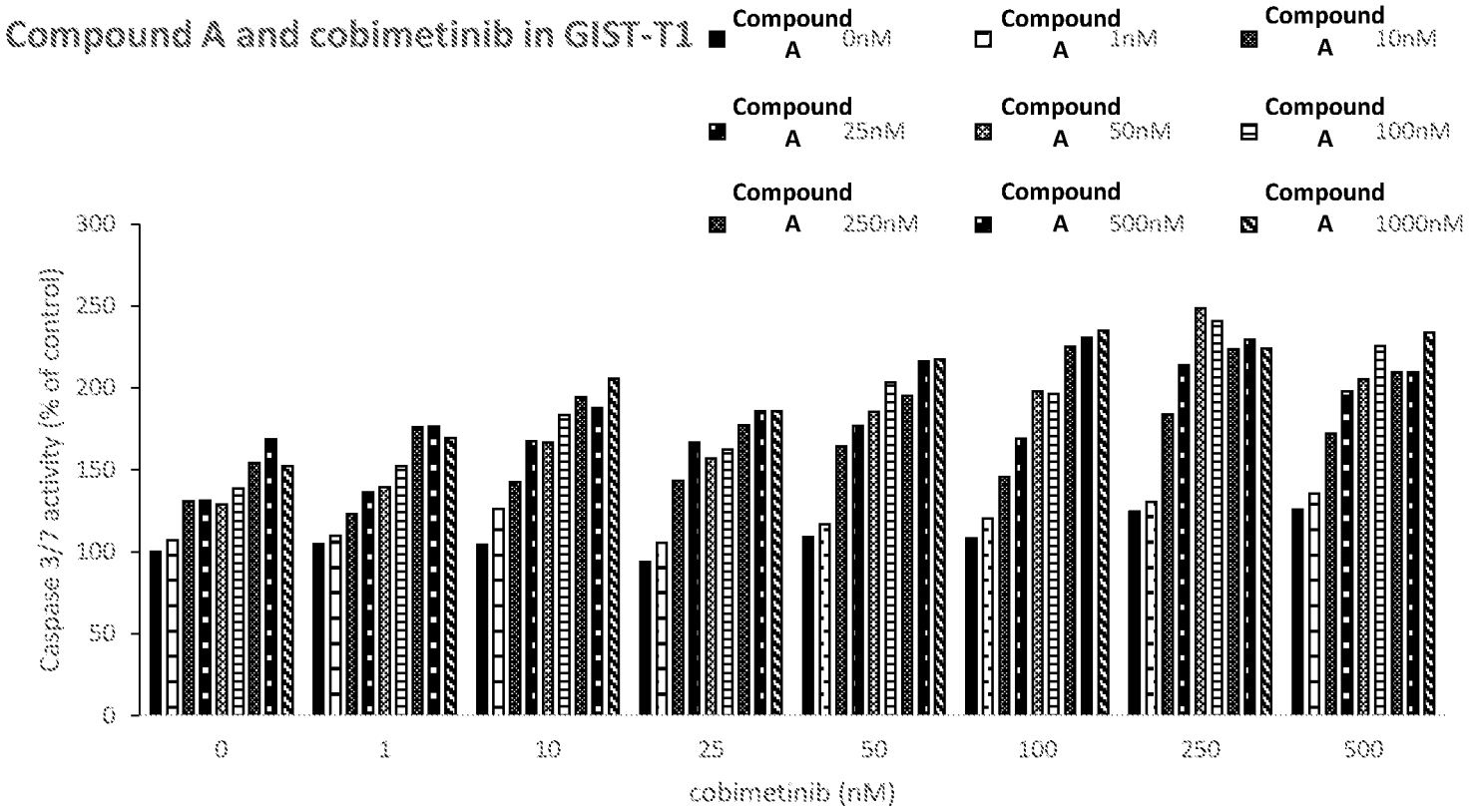


FIG. 5B **Combination index by Chou Talalay analysis**

CI<1 = synergy
CI=1 = additive effect
CI>1 = antagonism

CI	Compound A 1nM	Compound A 10nM	Compound A 25nM	Compound A 50nM	Compound A 100nM	Compound A 200nM	Compound A 500nM	Compound A 1000nM
Cobimetinib 1 nM	0.79708	1.31592	0.55315	0.75613	0.30708	0.04872	0.09745	0.42662
Cobimetinib 10 nM	0.0855	0.0977	0.01338	0.02833	0.00855	0.0069	0.02772	0.00822
Cobimetinib 25 nM	3.4939	0.09192	0.01338	0.08493	0.0949	0.04362	0.03441	0.06882
Cobimetinib 50 nM	0.50545	0.00754	0.00461	0.00363	0.00107	0.00621	0.00138	0.00249
Cobimetinib 100 nM	0.34962	0.0678	0.01067	9.52E-04	0.00223	2.74E-04	3.13E-04	4.17E-04
Cobimetinib 250 nM	0.08223	8.55E-04	8.95E-05	5.31E-06	2.27E-05	3.37E-04	3.47E-04	0.00122
Cobimetinib 500 nM	0.04575	0.00305	4.76E-04	4.33E-04	1.04E-04	0.00135	0.00271	4.62E-04

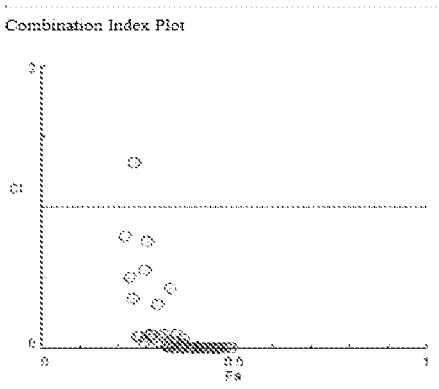


FIG. 5C

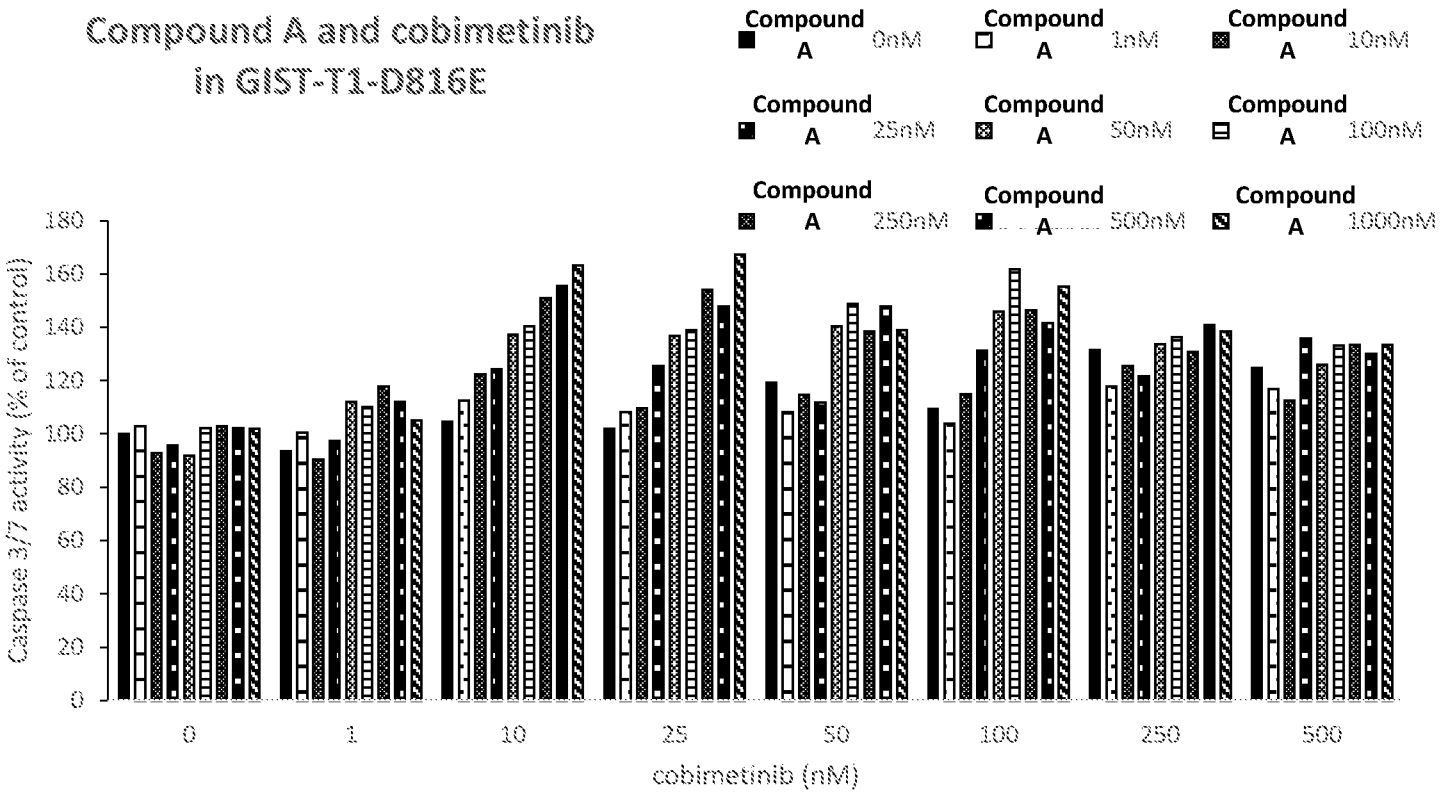


FIG. 5D **Combination index by Chou Talalay analysis**

CI<1 = synergy
CI=1 = additive effect
CI>1 = antagonism

CI	Compound A 1nM	Compound A 10nM	Compound A 25nM	Compound A 50nM	Compound A 100nM	Compound A 200nM	Compound A 500nM	Compound A 1000nM
Cobimetinib 1 nM	0.18534	438696	4.76549	0.02461	0.03479	0.00915	0.02461	0.08008
Cobimetinib 10 nM	0.23568	0.04233	0.03138	0.00324	0.00193	3.04E-04	1.35E-04	3.08E-05
Cobimetinib 25 nM	1.17886	0.94861	0.0607	0.00882	0.00598	4.44E-04	0.00129	3.77E-05
Cobimetinib 50 nM	2.46263	0.79943	1.28476	0.00963	0.00227	0.01361	0.00259	0.01248
Cobimetinib 100 nM	10.3649	1.46703	0.09078	0.00705	4.08E-04	0.00675	0.01549	0.00135
Cobimetinib 250 nM	2.28677	0.60705	1.15264	0.15427	0.09612	0.25807	0.04413	0.06806
Cobimetinib 500 nM	5.42979	11.784	0.20954	1.11463	0.33621	0.30855	0.56228	0.30855

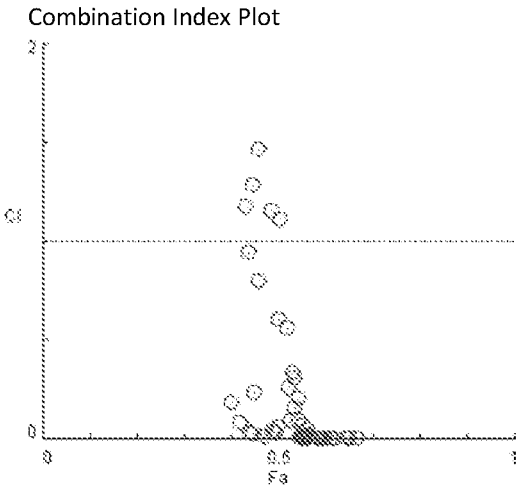


FIG. 5E

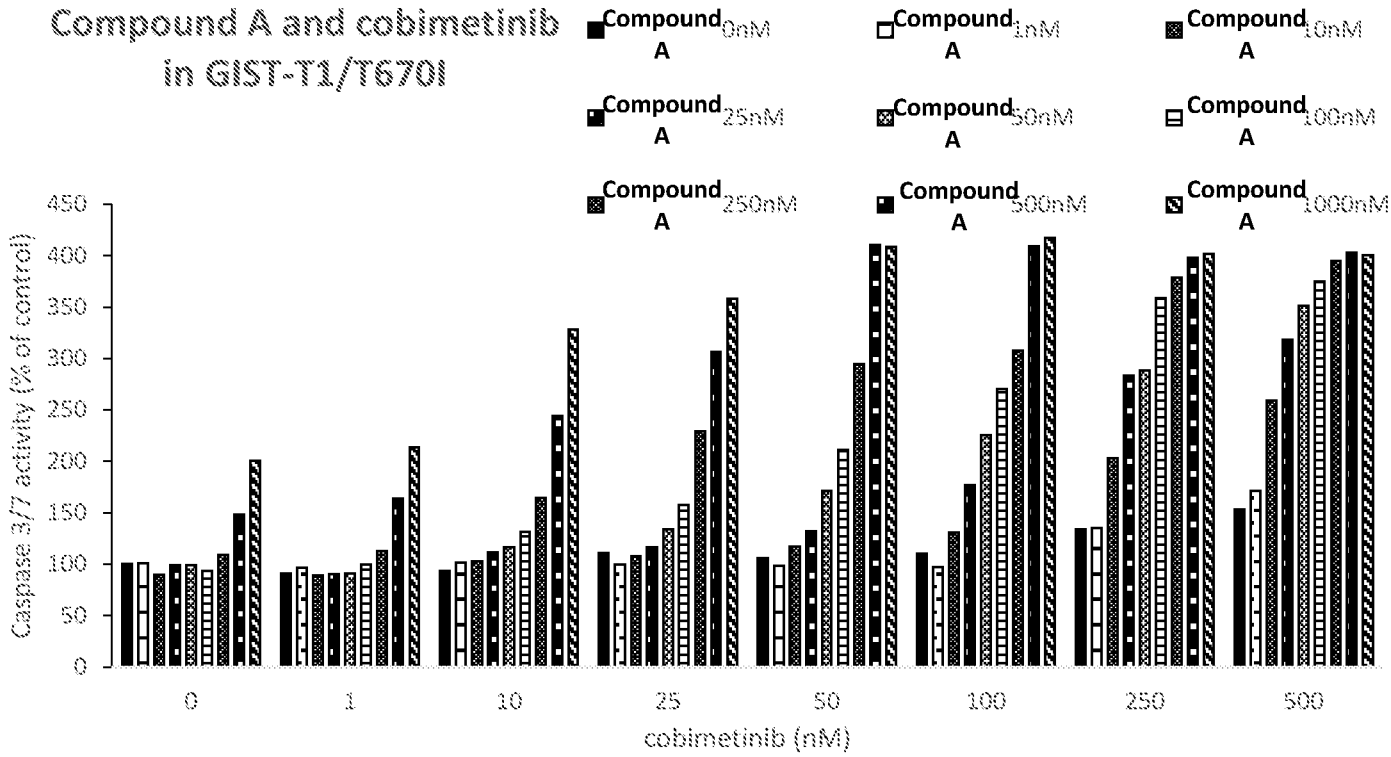


FIG. 5F

Combination index by Chou Talalay analysis

CI<1 = synergy
CI=1 = additive effect
CI>1 = antagonism

CI	Compound A 1nM	Compound A 10nM	Compound A 25nM	Compound A 50nM	Compound A 100nM	Compound A 200nM	Compound A 500nM	Compound A 1000nM
Cobimetinib 1 nM	0.26554	2.67726	5.76653	10.5467	7.71672	4.89163	0.13285	0.0072
Cobimetinib 10 nM	0.9985	1.33769	0.84391	0.86036	0.39351	0.06559	4.54E-04	2.51E-06
Cobimetinib 25 nM	2.8673	1.43276	0.75657	0.22264	0.04996	6.46E-04	6.27E-06	2.47E-07
Cobimetinib 50 nM	6.77934	0.90654	0.2524	0.01232	0.00104	7.27E-06	8.00E-10	1.99E-09
Cobimetinib 100 nM	16.1737	0.4255	0.00853	2.79E-04	1.89E-05	3.10E-06	9.50E-10	7.40E-10
Cobimetinib 250 nM	0.62392	0.0019	5.23E-06	4.56E-06	3.00E-08	1.07E-08	3.20E-09	4.13E-09
Cobimetinib 500 nM	0.04617	5.14E-05	5.56E-07	4.53E-08	1.19E-09	2.52E-09	1.94E-09	5.19E-09

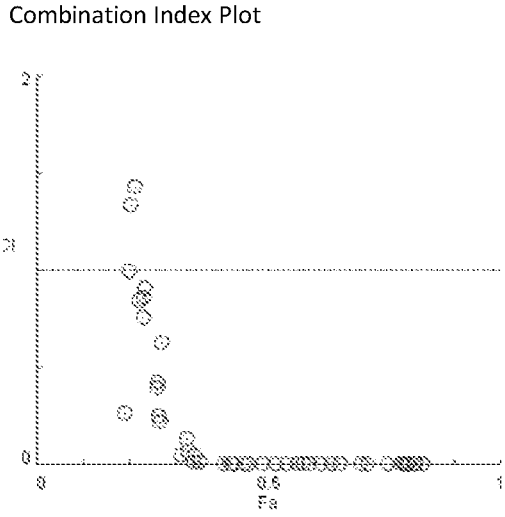


FIG. 6A

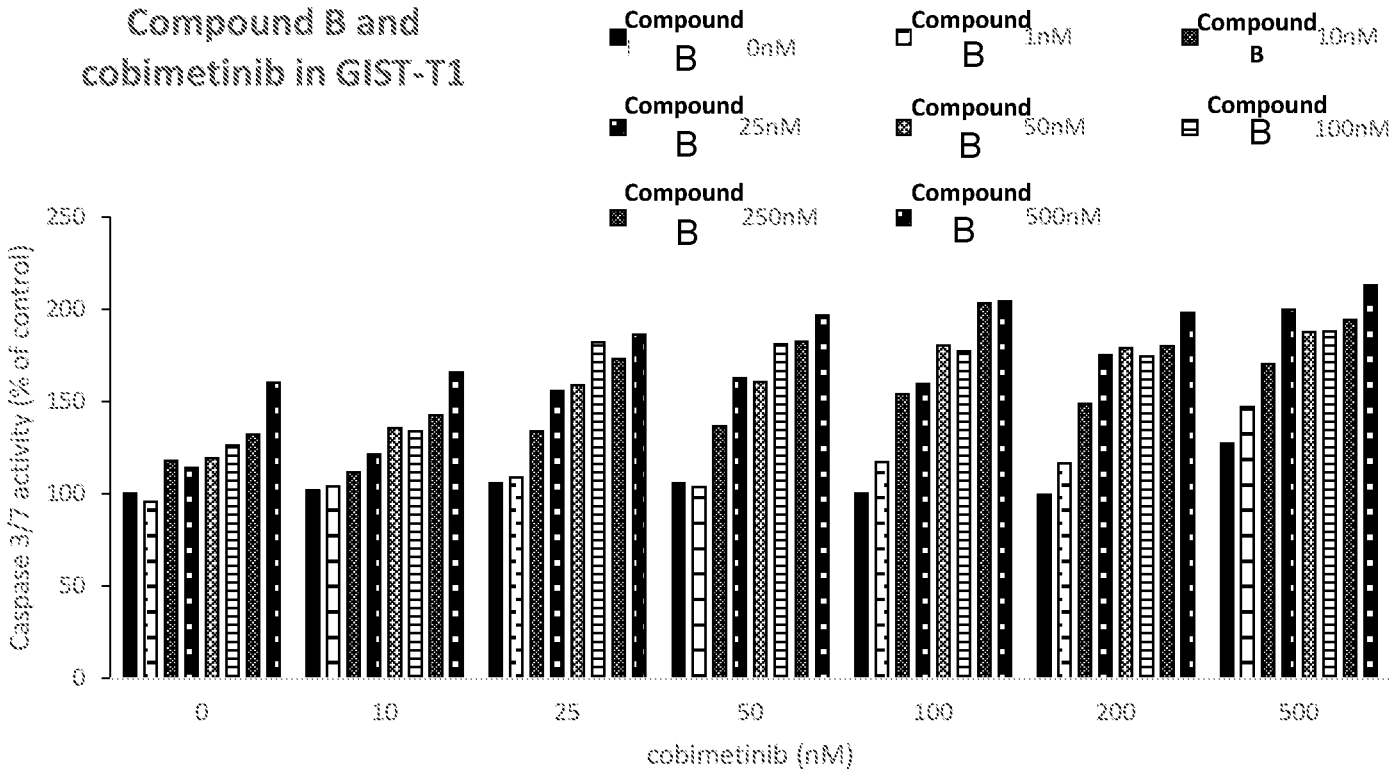


FIG. 6B

Combination index by Chou Talalay analysis

CI<1 = synergy
CI=1 = additive effect
CI>1 = antagonism

CI	Compound B 1nM	Compound B 10nM	Compound B 25nM	Compound B 50nM	Compound B 100nM	Compound B 200nM	Compound B 500nM
Cobimetinib 10 nM	0.56205	1.23447	0.95172	0.33923	0.8499	0.57466	0.05953
Cobimetinib 25 nM	0.37301	0.08307	0.01254	0.01607	0.000825	0.00764	0.00181
Cobimetinib 50 nM	1.76547	0.06105	0.00477	0.01282	0.000975	0.00158	0.0002
Cobimetinib 100 nM	0.17549	0.00644	0.0073	0.000551	0.00193	1.34E-05	2.54E-05
Cobimetinib 200 nM	0.3168	0.01266	0.000656	0.000703	0.00317	0.00249	0.000126
Cobimetinib 500 nM	0.00186	0.000613	4.14E-06	0.000144	0.000251	0.000131	8.3E-07

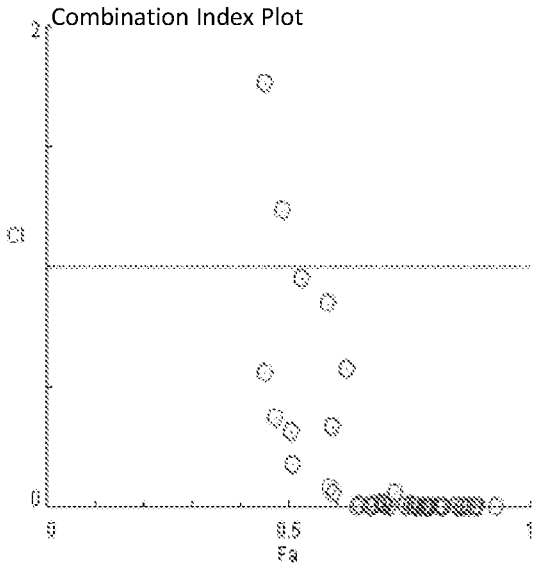


FIG. 6C

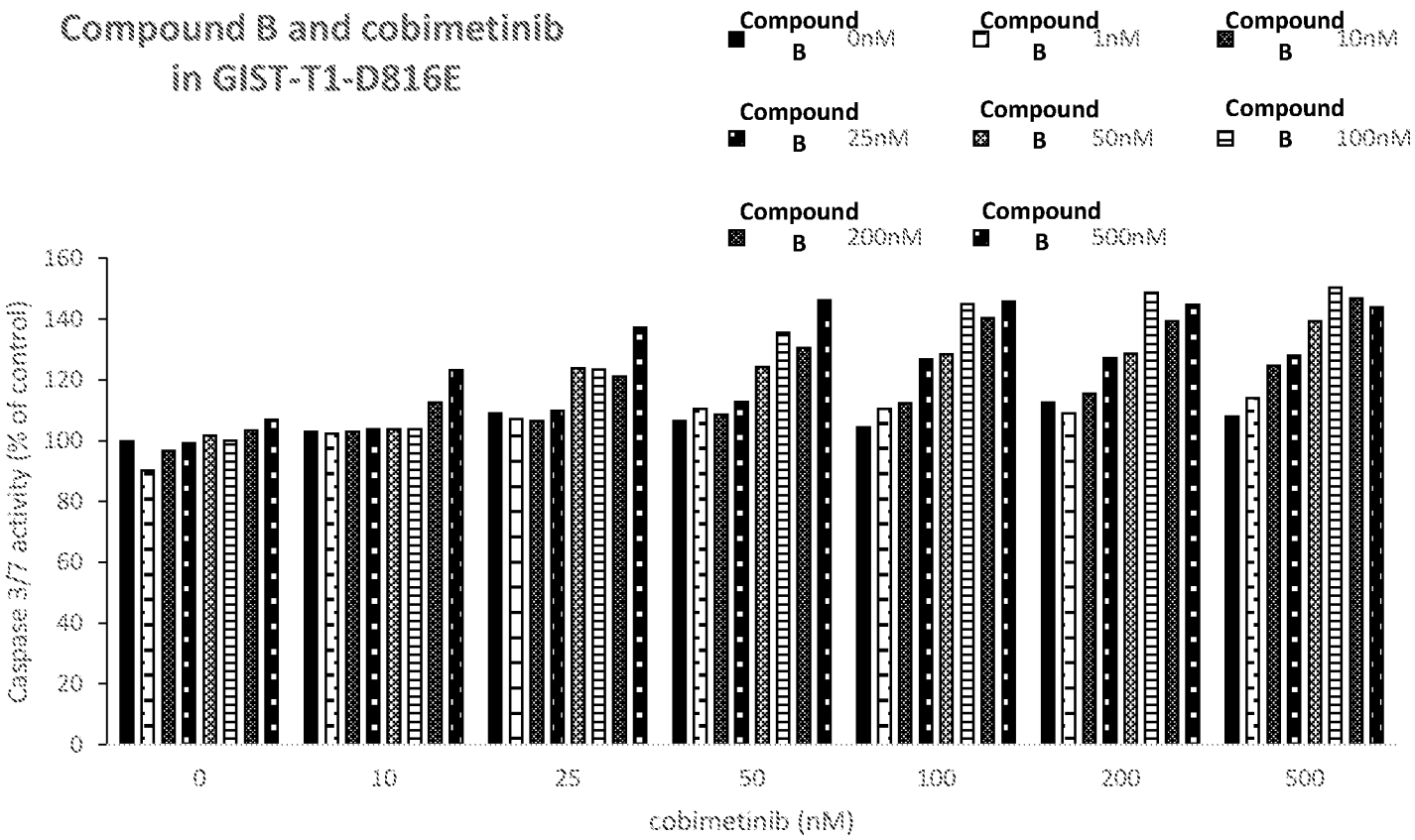


FIG. 6D

Combination index by Chou Talalay analysis

CI<1 = synergy
CI=1 = additive effect
CI>1 = antagonism

CI	Compound B 1nM	Compound B 10nM	Compound B 25nM	Compound B 50nM	Compound B 100nM	Compound B 200nM	Compound B 500nM
Cobimetinib 10 nM	1.78658	1.4423	33.0169	1.15037	7.15955	0.03569	0.000619
Cobimetinib 25 nM	0.37205	0.54877	0.09771	7.19E-05	0.000137	0.000781	3.5E-07
Cobimetinib 50 nM	0.12042	0.36756	0.0391	8.29E-05	2.14E-07	6.79E-06	7.2E-10
Cobimetinib 100 nM	0.24051	0.09661	2.61E-05	1.04E-05	4.2E-10	2.11E-08	1.07E-09
Cobimetinib 200 nM	1.00074	0.03502	3.02E-05	1.47E-05	1.8E-11	3.89E-08	2.34E-09
Cobimetinib 500 nM	0.1855	0.000379	4.48E-05	1.86E-08	4.1E-12	1.8E-10	3.97E-09

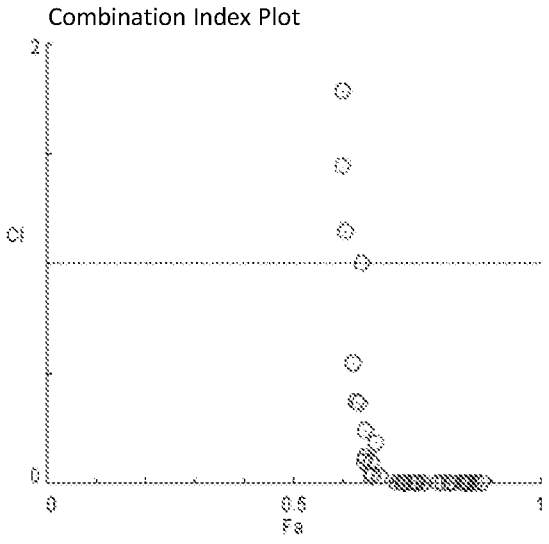


FIG. 6E

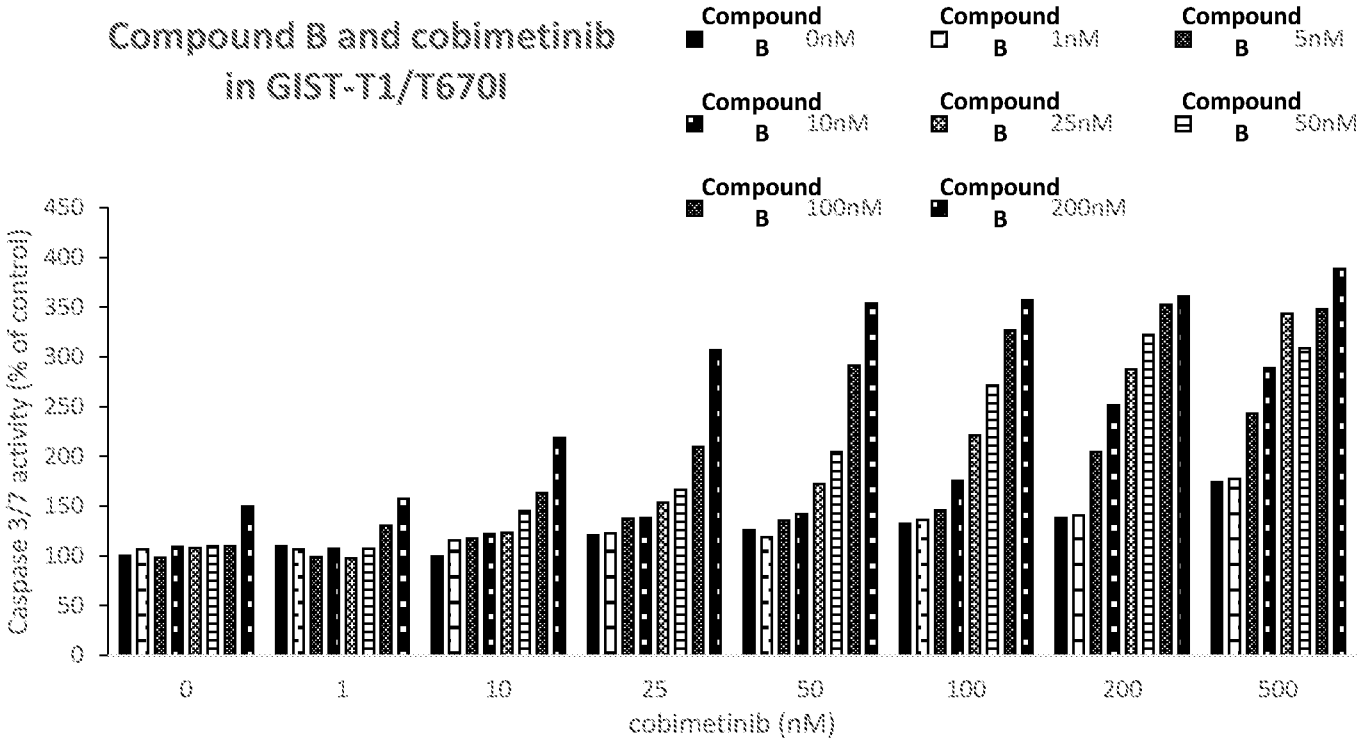


FIG. 6F

Combination index by Chou Talalay analysis

CI<1 = synergy
CI=1 = additive effect
CI>1 = antagonism

CI	Compound B 1nM	Compound B 5nM	Compound B 10nM	Compound B 25nM	Compound B 50nM	Compound B 100nM	Compound B 200nM
Cobimetinib 1 nM	0.41369	3.735	1.55347	21.4235	6.74637	0.24978	0.00783
Cobimetinib 10 nM	1.03215	0.85167	0.54699	0.59718	0.05047	0.00877	6.73E-05
Cobimetinib 25 nM	1.09419	0.2284	0.22022	0.04847	0.0152	3.62E-04	1.23E-07
Cobimetinib 50 nM	3.39319	0.55609	0.29001	0.01725	0.00105	8.66E-07	3.52E-09
Cobimetinib 100 nM	1.04878	0.40707	0.02628	5.35E-04	9.31E-06	8.64E-08	5.25E-09
Cobimetinib 200 nM	1.33157	0.00418	9.39E-05	5.03E-06	2.57E-07	1.63E-08	6.70E-09
Cobimetinib 500 nM	0.10996	4.48E-04	1.11E-05	9.15E-08	2.16E-06	5.98E-08	8.60E-10

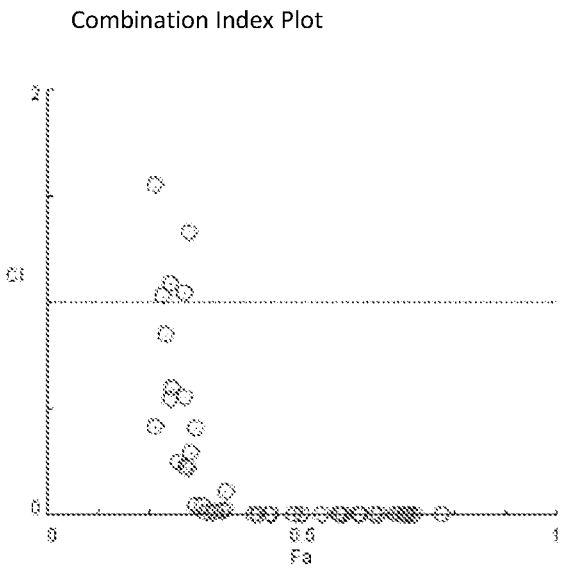


FIG. 7A

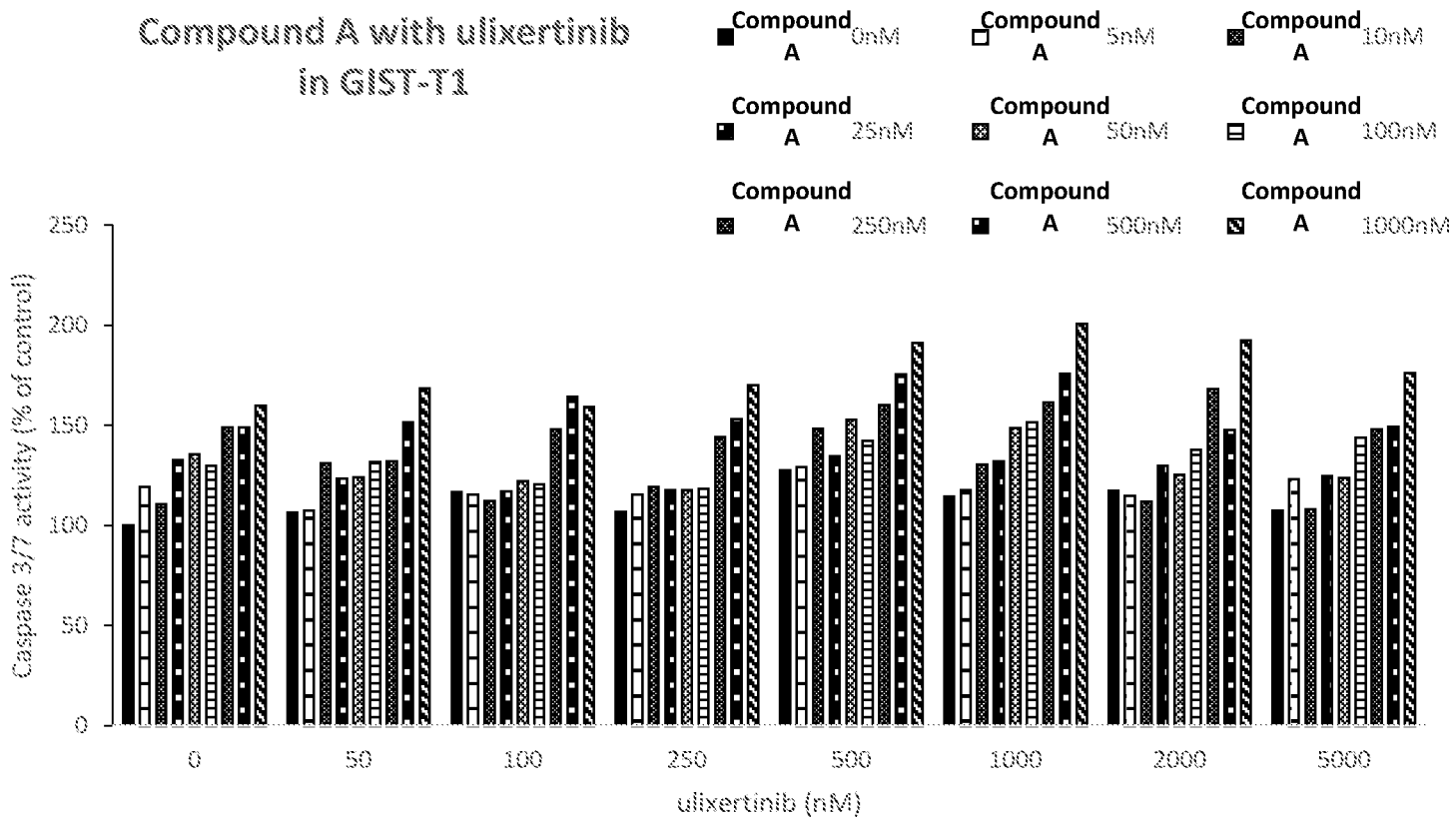


FIG. 7B

Combination index by Chou Talalay analysis

CI<1 = synergy
CI=1 = additive effect
CI>1 = antagonism

CI	Compound A 5nM	Compound A 5nM	Compound A 10nM	Compound A 25nM	Compound A 50nM	Compound A 100nM	Compound A 200nM	Compound A 500nM	Compound A 1000nM
Ulixertinib 50nM	397033	12152.7	0.29353	2.00594	3.73337	2.73202	6.357	0.83994	0.143
Ulixertinib 100nM	15.0853	1.23598	7.30524	4.9472	4.97932	12.3642	0.67675	0.13312	0.57025
Ulixertinib 250nM	1.3E+11	1.29932	1.48118	4.60126	9.20222	16.5094	1.16864	0.67302	0.1129
Ulixertinib 500nM	0.14288	0.18202	0.0261	0.44394	0.06984	0.60244	0.12257	0.0243	0.00367
Ulixertinib 1000nM	0.05213	0.92137	0.30425	0.6357	0.13049	0.16799	0.10139	0.02333	6.50E-04
Ulixertinib 2000nM	9233.7	1.87274	70.9971	0.84709	3.23328	1.15347	0.03718	1.45611	0.00291
Ulixertinib 5000nM	0.7266	0.43113	274131	1.73715	3.87011	0.50263	0.67675	1.12708	0.0448

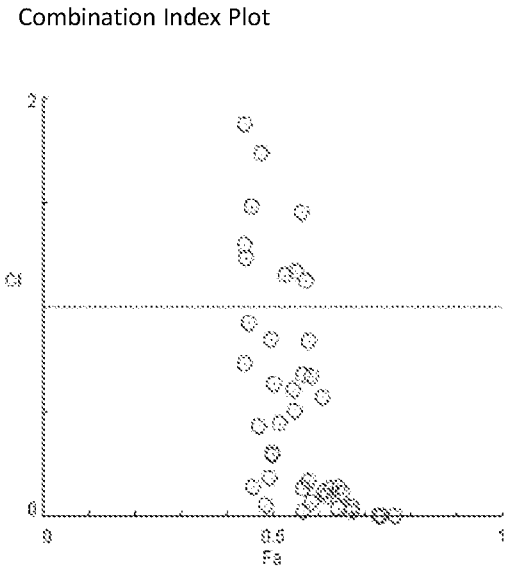


FIG. 7C

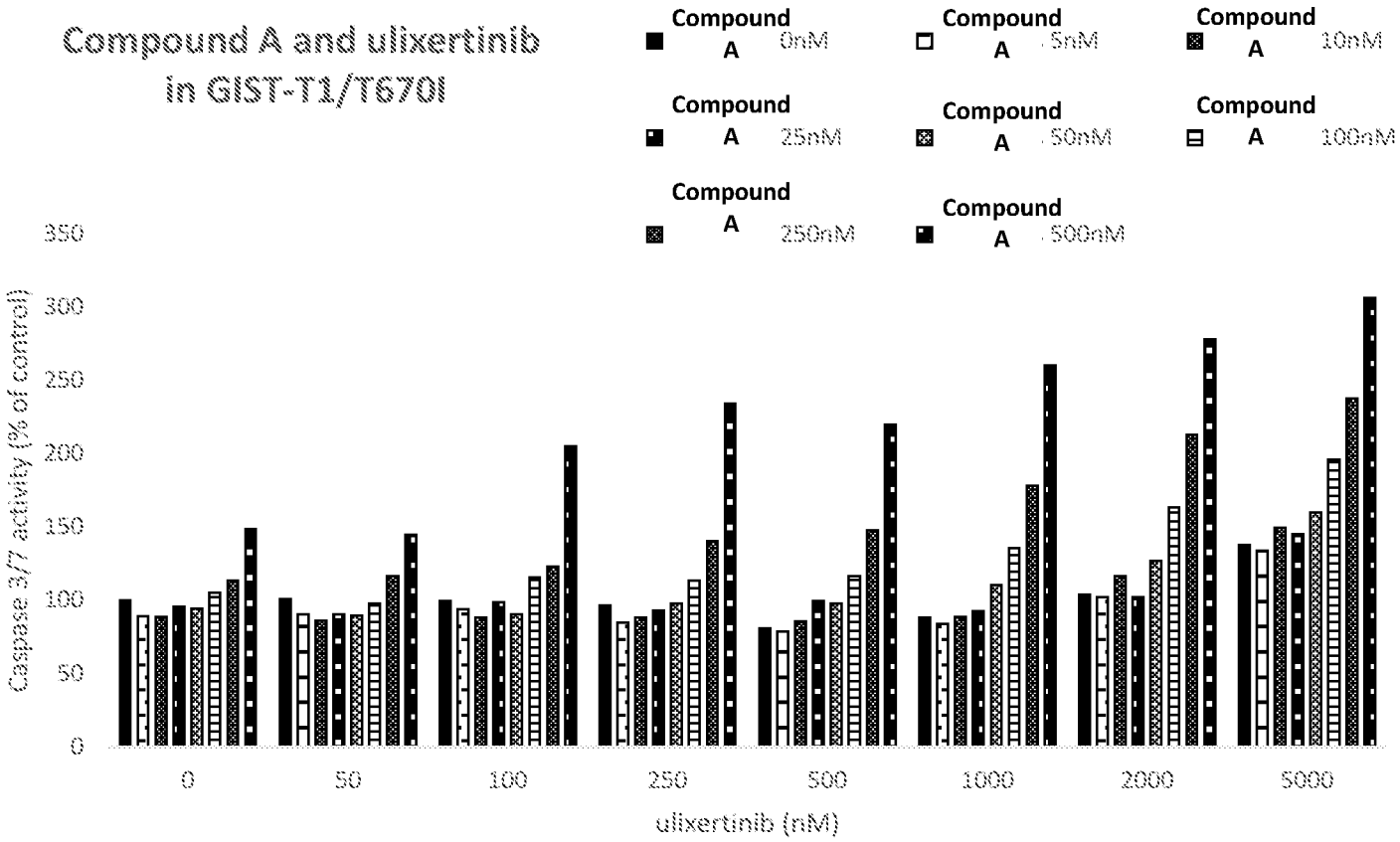


FIG. 7D

Combination index by Chou Talalay analysis

CI<1 = synergy
CI=1 = additive effect
CI>1 = antagonism

CI	Compound A 5nM	Compound A 10nM	Compound A 25nM	Compound A 50nM	Compound A 100nM	Compound A 200nM	Compound A 500nM
Ulixertinib 50nM	1.31834	3.57672	2.90308	5.56256	3.88493	1.36233	0.3461
Ulixertinib 100nM	1.10711	3.91925	1.11824	5.40429	0.75024	0.75332	0.00559
Ulixertinib 250nM	17.7013	8.33131	4.13239	2.71447	0.87632	0.19479	9.10E-04
Ulixertinib 500nM	175.181	27.9521	1.87828	0.83106	0.68648	0.11088	0.00217
Ulixertinib 1000nM	87.5534	27.0813	11.9376	3.57	0.14557	0.013	1.83E-04
Ulixertinib 2000nM	2.74177	0.20886	3.54357	0.1633	0.01821	0.00135	6.21E-05
Ulixertinib 5000nM	0.02425	0.00614	0.01896	0.01184	0.00199	2.93E-04	9.86E-06

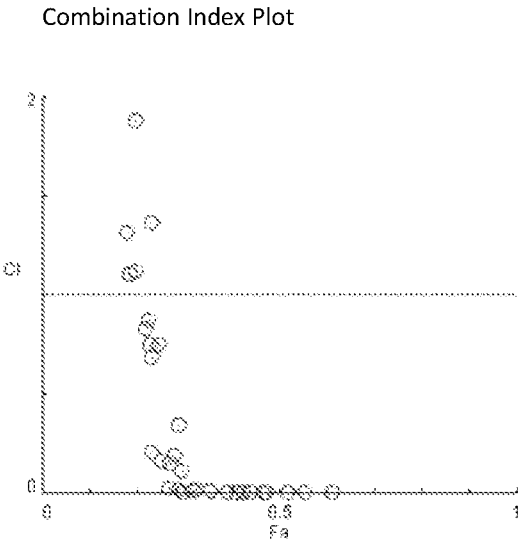


FIG. 8A

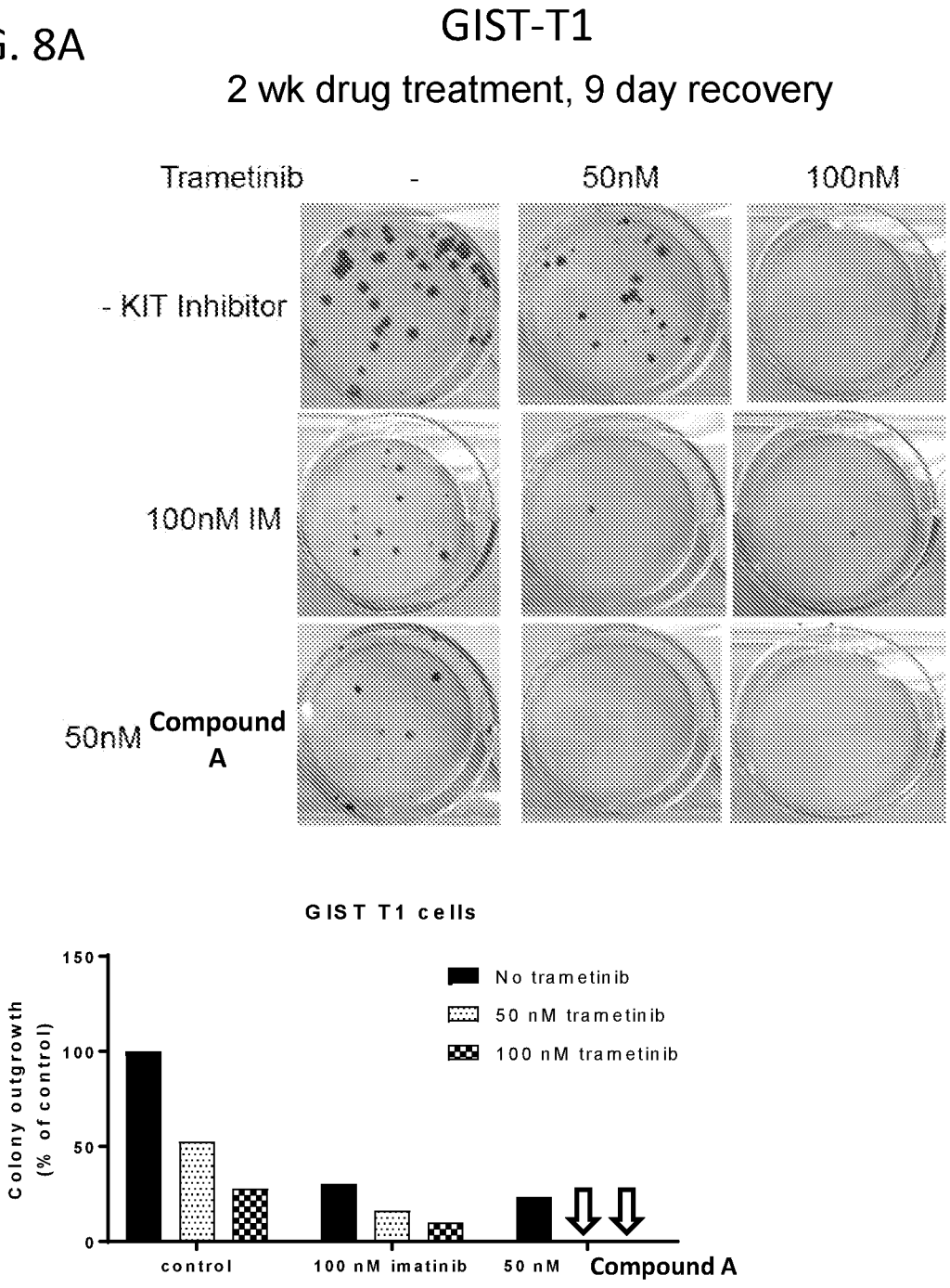
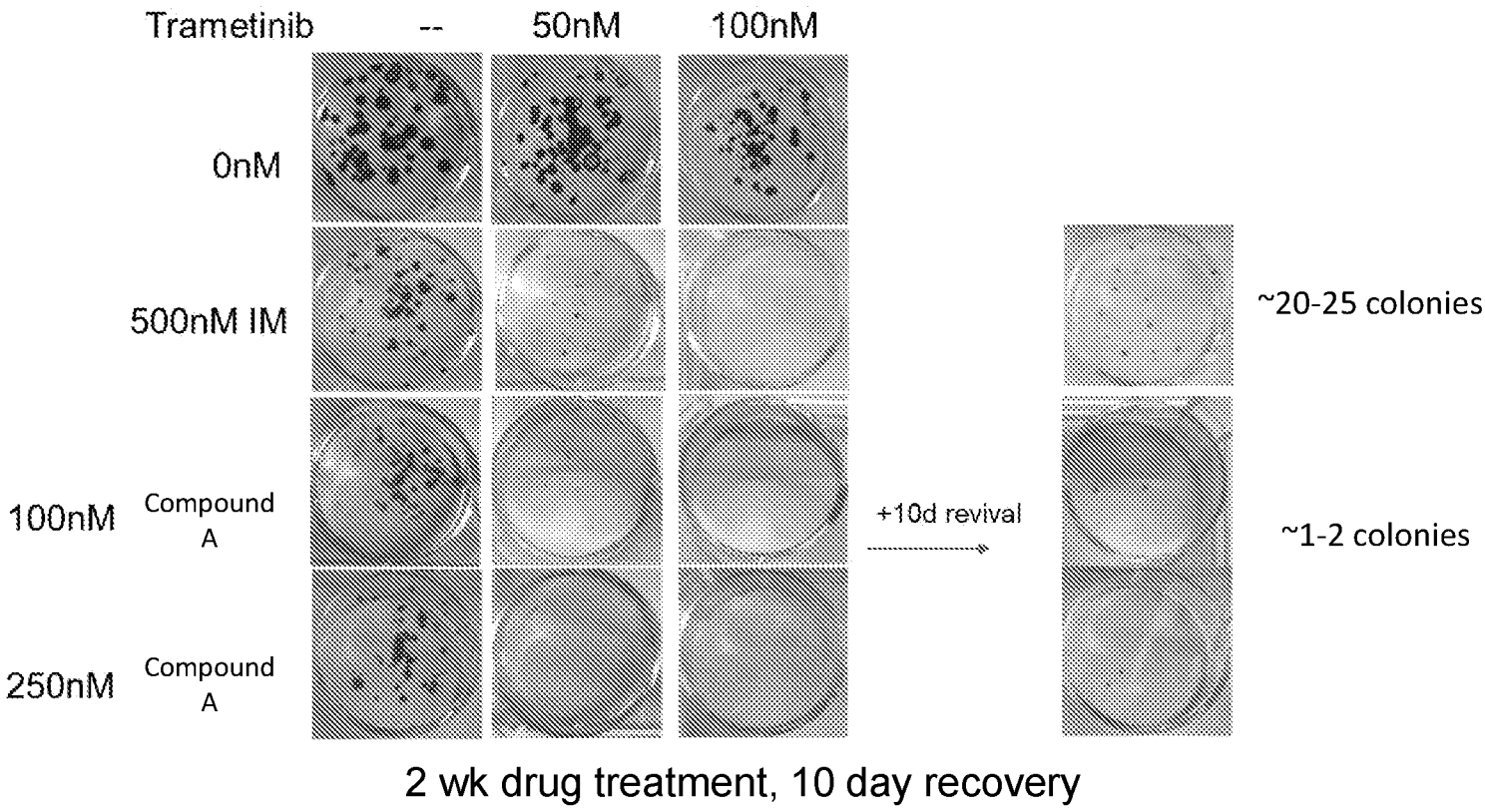
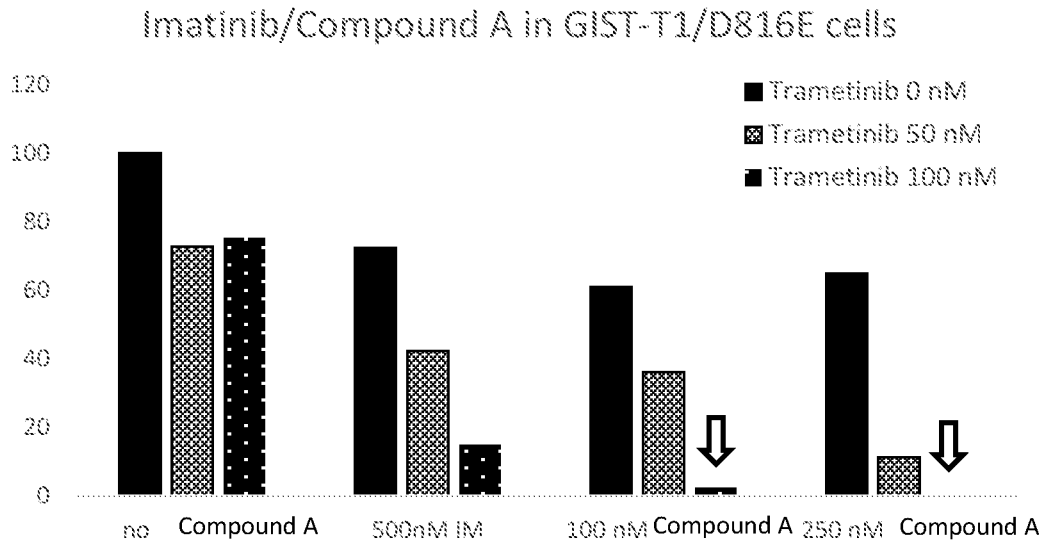

GIST-T1
2 wk drug treatment, 9 day recovery
Trametinib
-
50nM
100nM
- KIT Inhibitor
100nM IM
50nM
Compound A
GIST T1 cells
Colony outgrowth (% of control)
150
100
50
0
No trametinib
50 nM trametinib
100 nM trametinib
control
100 nM imatinib
50 nM
Compound A

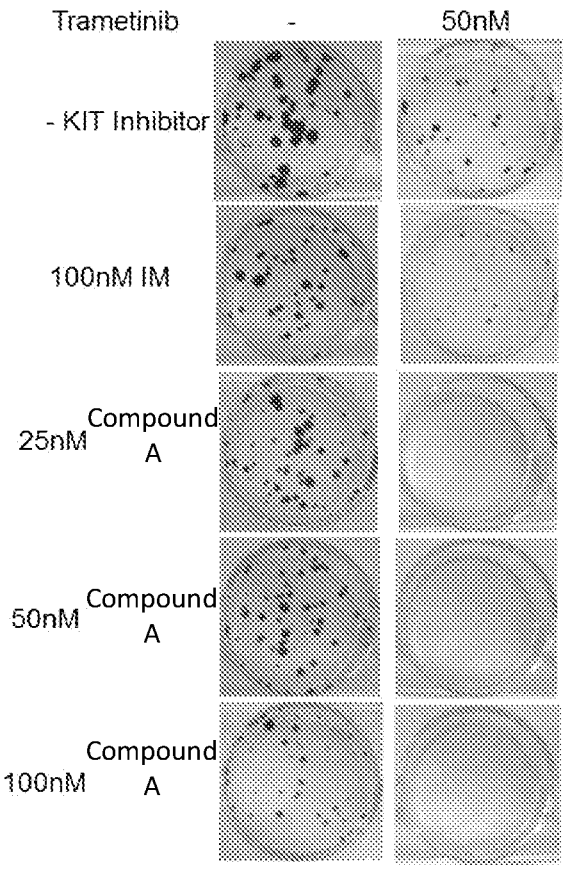
FIG. 8B


GIST-T1/D816E
Trametinib
--
50nM
100nM
0nM
500nM IM
100nM
Compound A
250nM
Compound A
+10d revival
~20-25 colonies
~1-2 colonies
2 wk drug treatment, 10 day recovery


Imatinib/Compound A in GIST-T1/D816E cells
Trametinib 0 nM
Trametinib 50 nM
Trametinib 100 nM
120
100
80
60
40
20
0
no
Compound A
500nM IM
100 nM
Compound A
250 nM
Compound A

GIST-T1/D816E

FIG. 8C



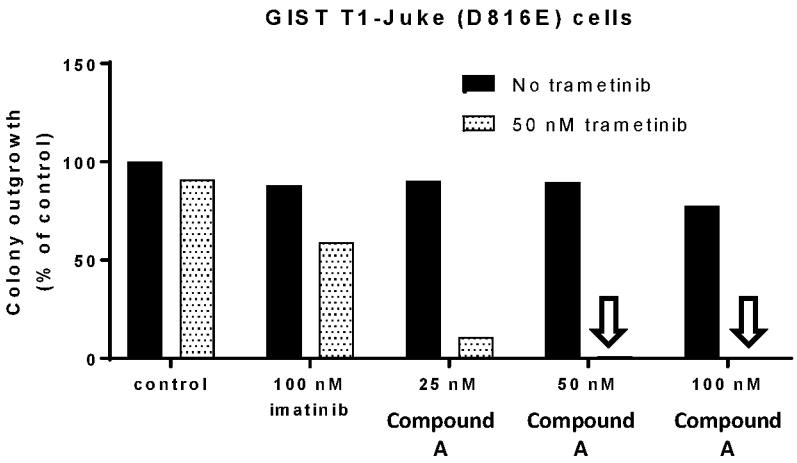
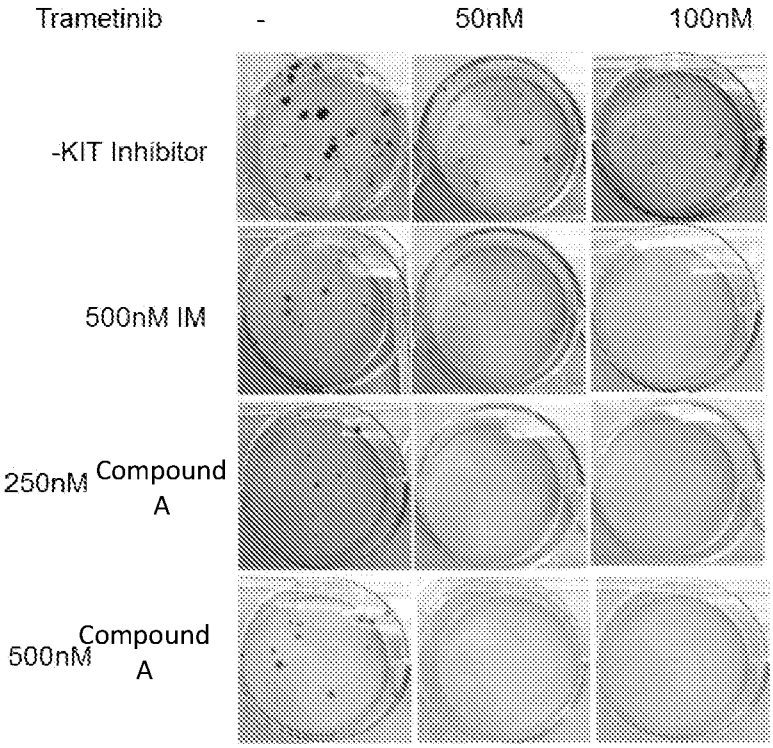
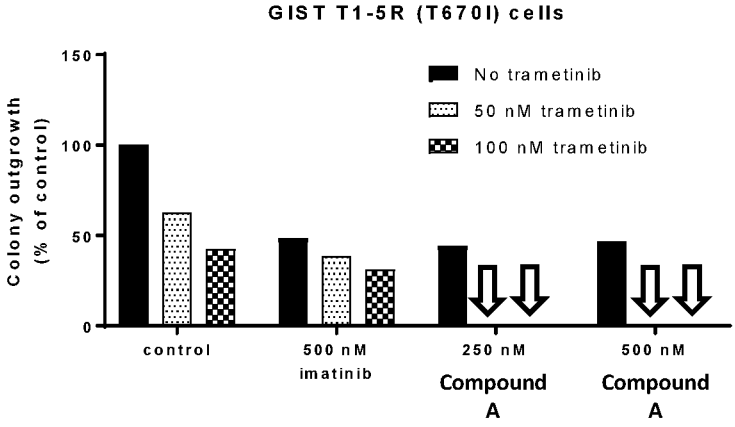


FIG. 8D

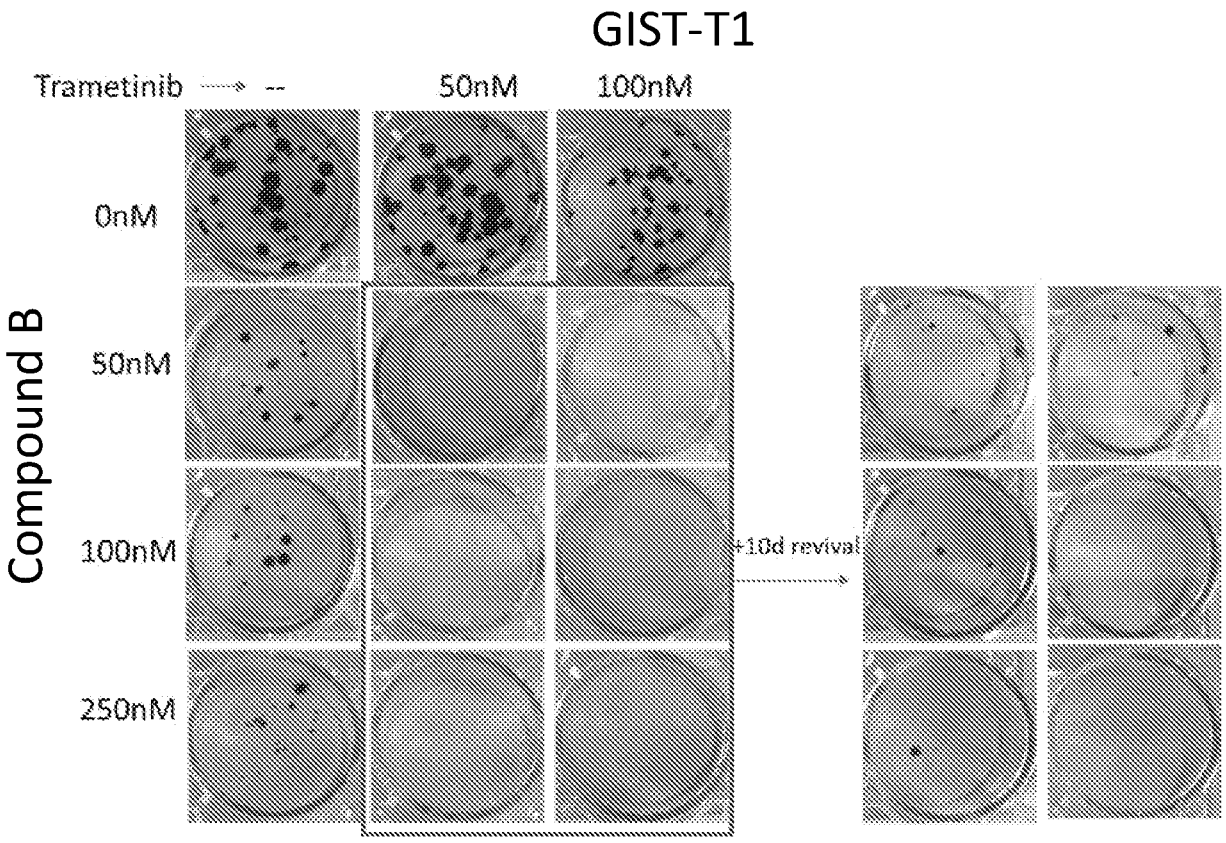
GIST-T1/T670I





2 wk drug treatment, 10 day recovery

Fig. 9A


GIST-T1
Trametinib
--
50nM
100nM
Compound B
0nM
50nM
100nM
250nM
+10d revival

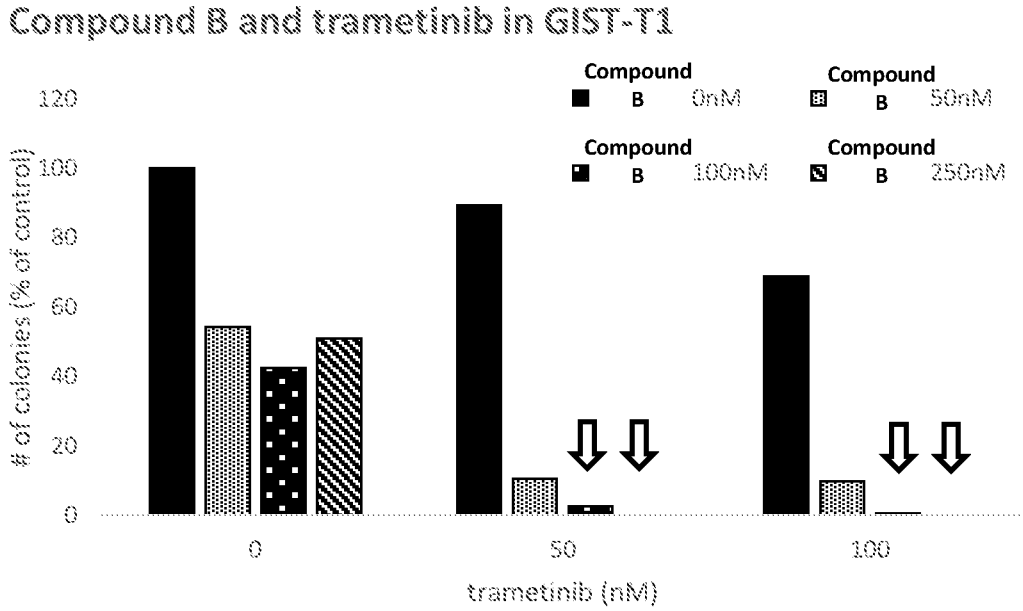
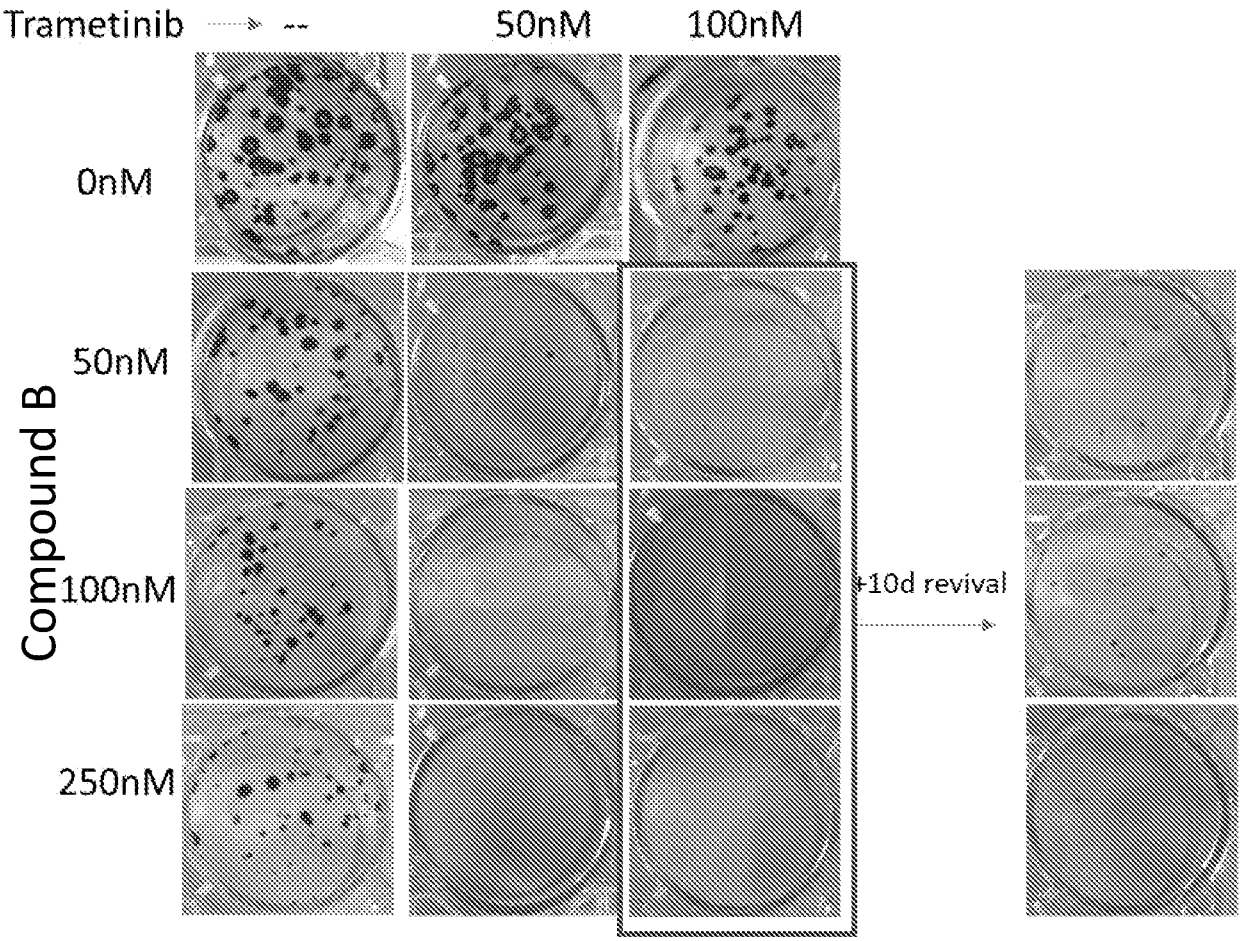

Compound B and trametinib in GIST-T1
Compound B 0nM
Compound B 50nM
Compound B 100nM
Compound B 250nM
# of colonies (% of control)
120
100
80
60
40
20
0
0
50
100
trametinib (nM)

Fig. 9B

GIST-T1/D816E



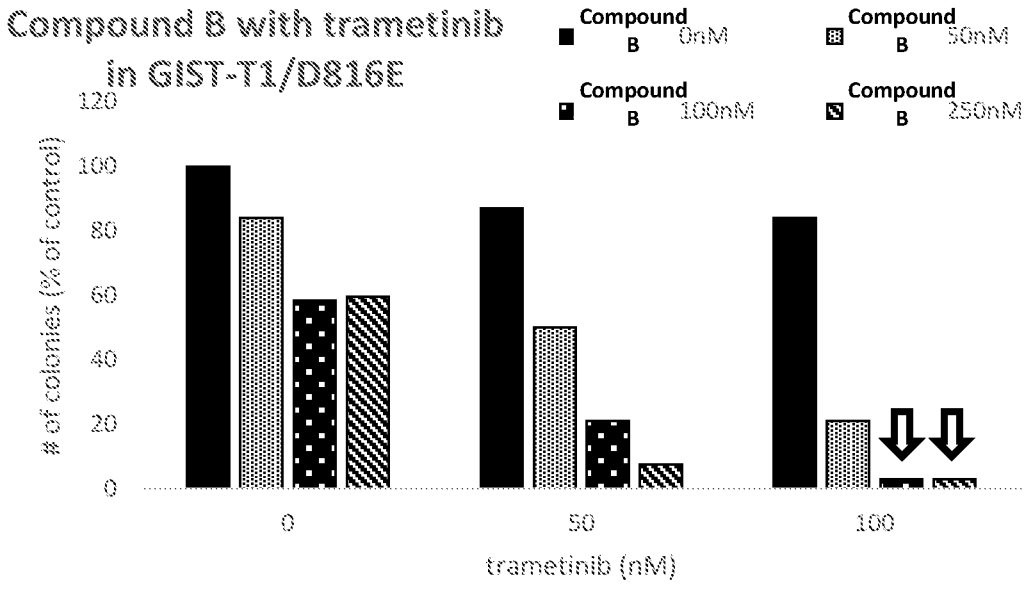


Fig. 9C

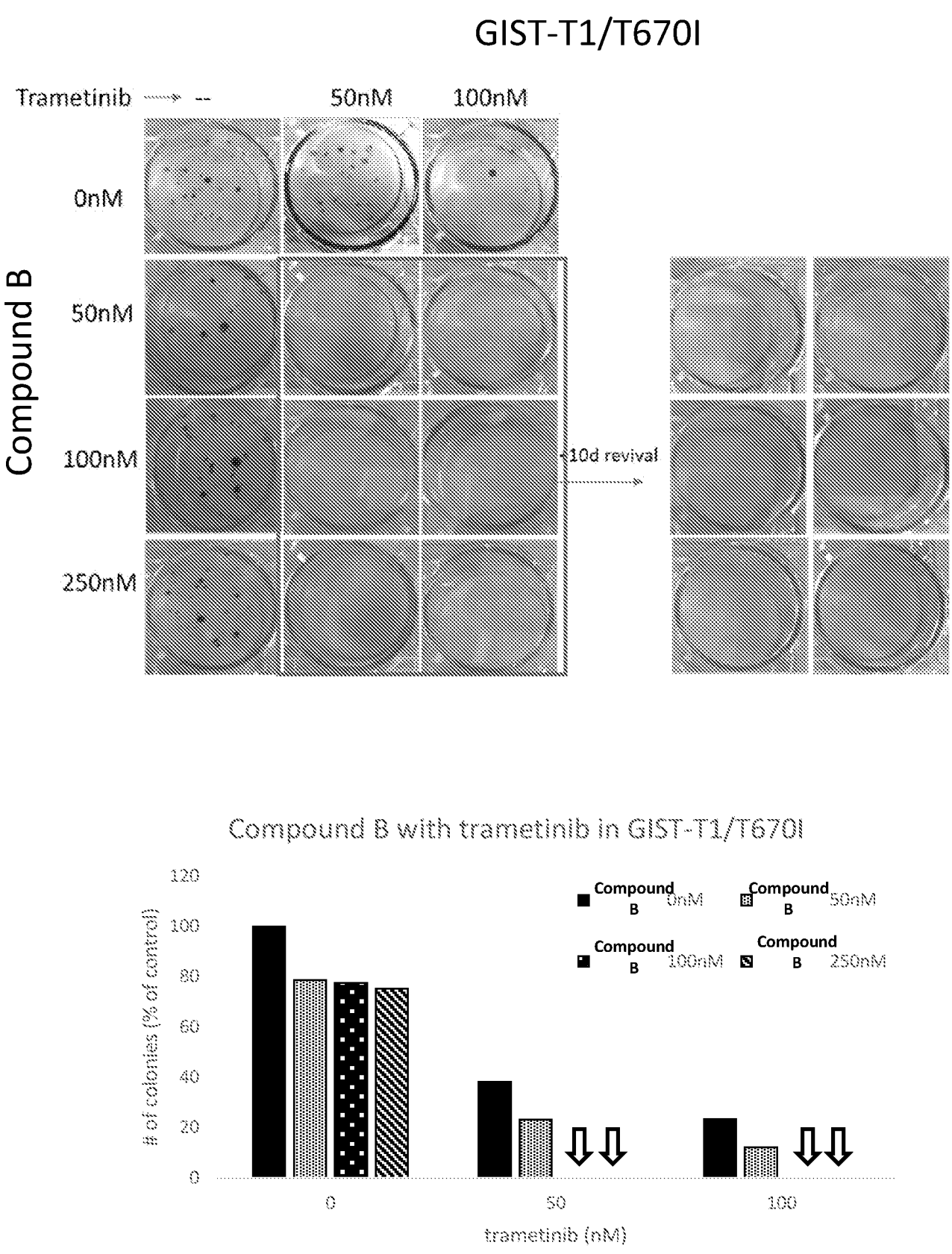
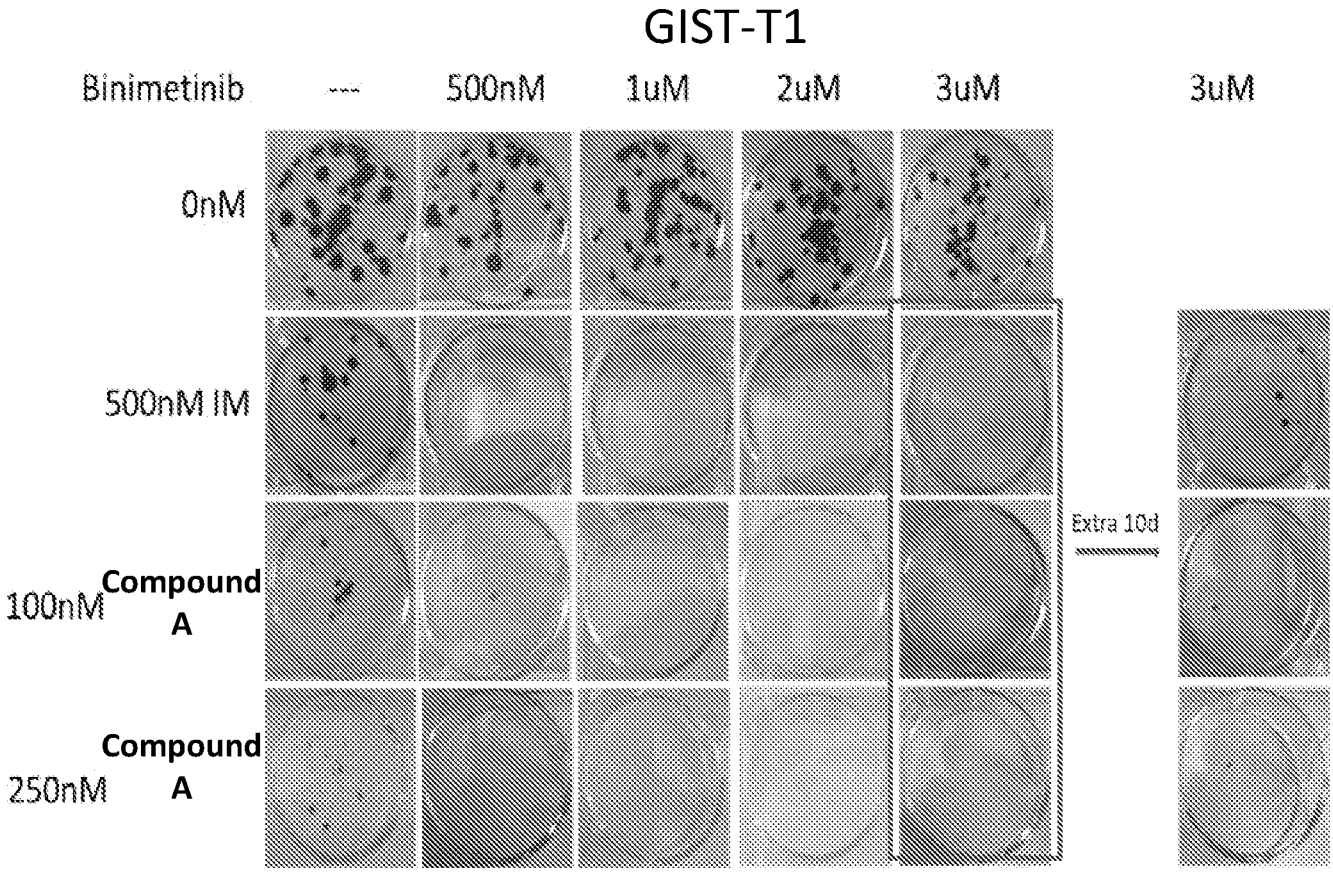

GIST-T1/T670I
Trametinib
--
50nM
100nM
0nM
50nM
100nM
250nM
Compound B
10d revival
Compound B with trametinib in GIST-T1/T670I
# of colonies (% of control)
120
100
80
60
40
20
0
Compound B 0nM
Compound B 50nM
Compound B 100nM
Compound B 250nM
0
50
100
trametinib (nM)

Fig. 10A


GIST-T1
Binimetinib

500nM
1uM
2uM
3uM
3uM
0nM
500nM IM
100nM
Compound A
250nM
Compound A
Extra 10d

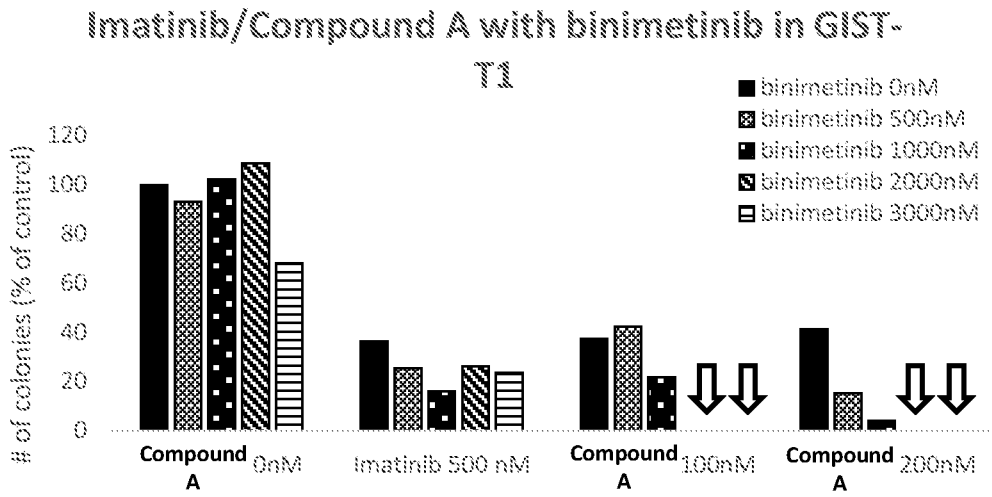
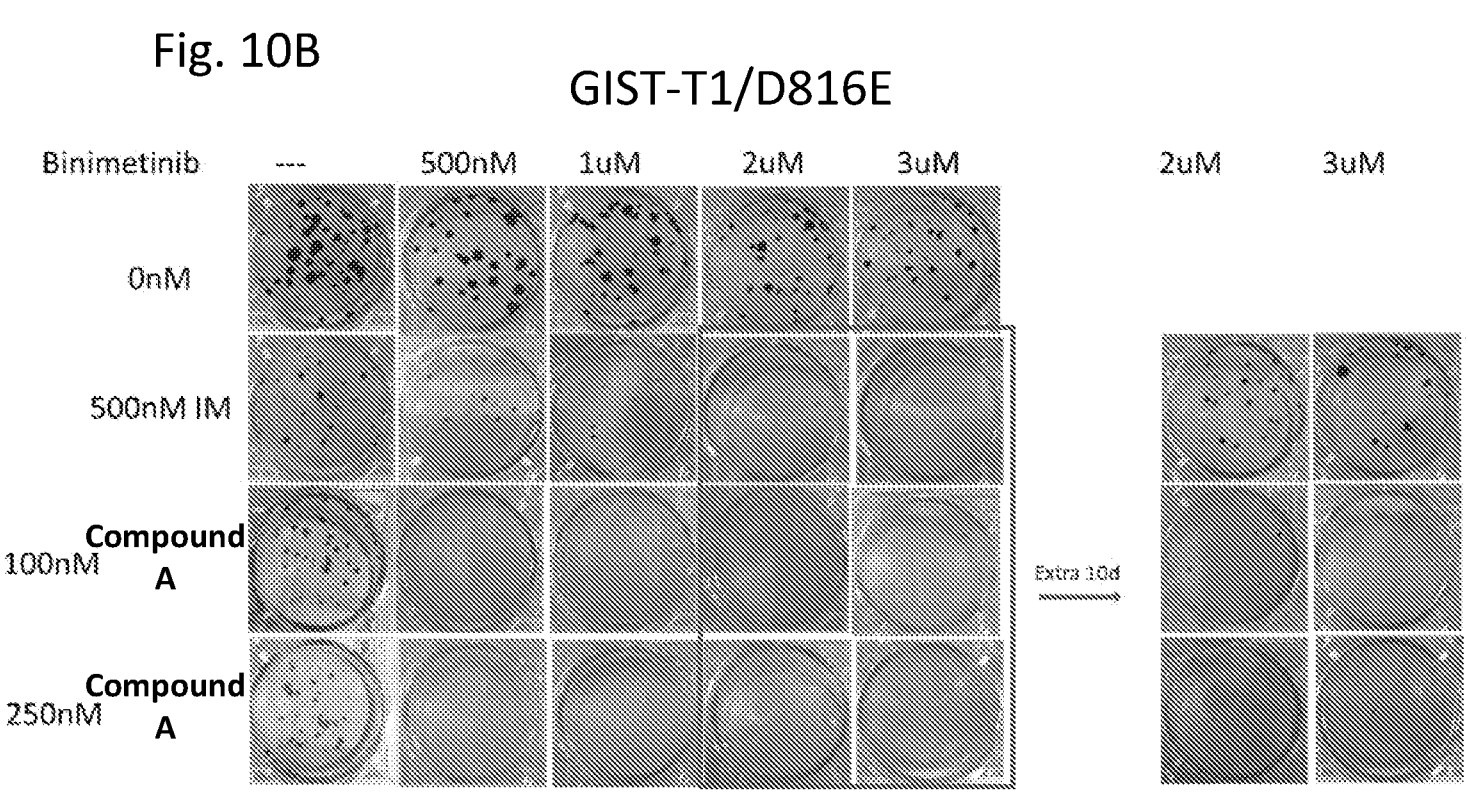

Imatinib/Compound A with binimetinib in GIST-T1
binimetinib 0nM
binimetinib 500nM
binimetinib 1000nM
binimetinib 2000nM
binimetinib 3000nM
# of colonies (% of control)
120
100
80
60
40
20
0
Compound A
0nM
Imatinib 500 nM
Compound A
100nM
Compound A
200nM

Fig. 10B


GIST-T1/D816E
Binimetinib

500nM
1uM
2uM
3uM
2uM
3uM
0nM
500nM IM
Compound A
100nM
Compound A
250nM
Extra 10d

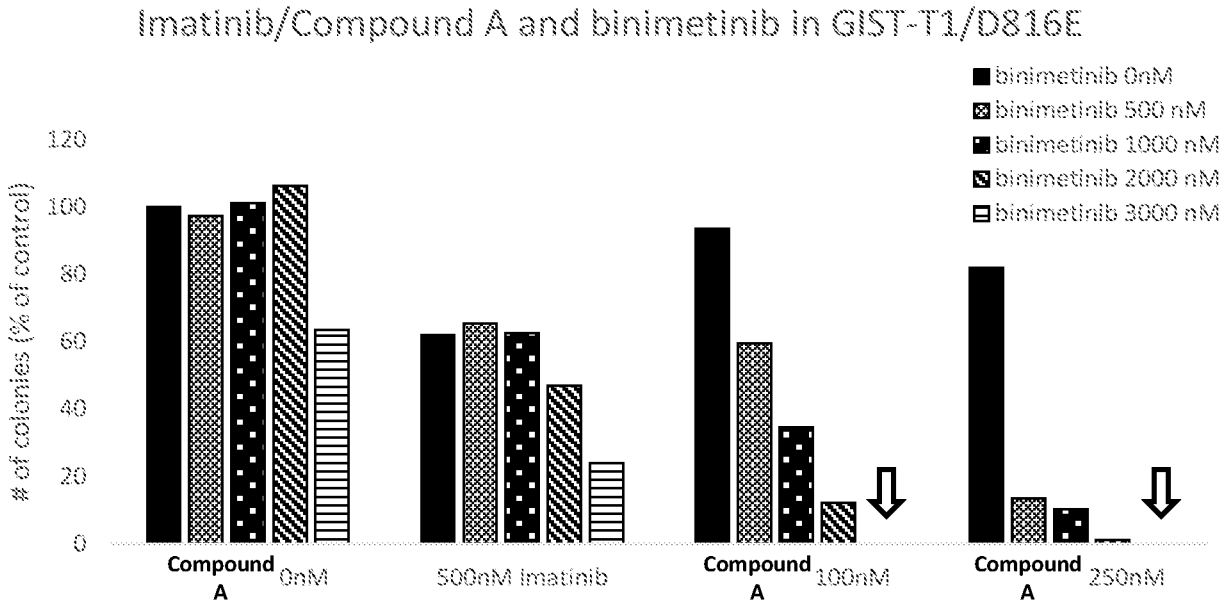
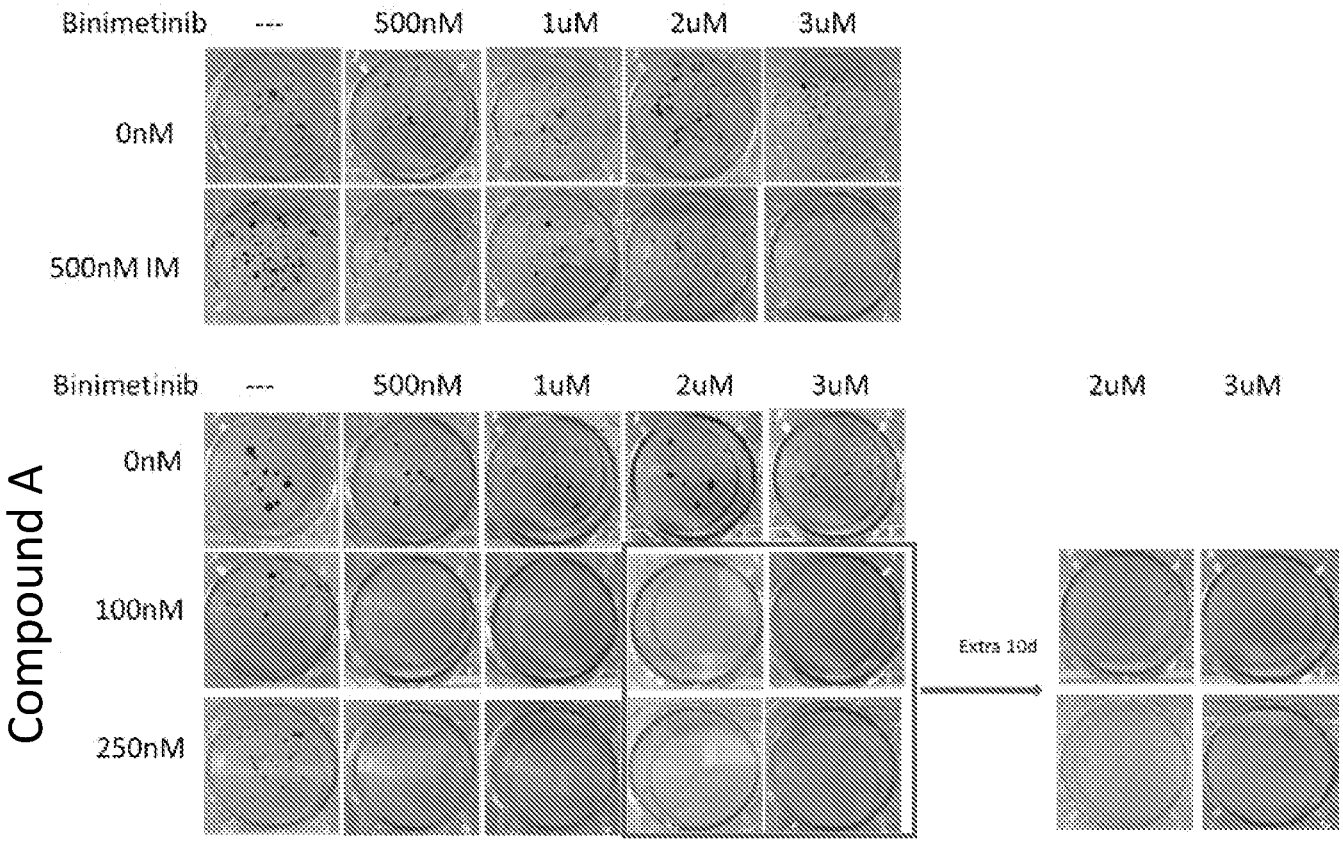

Imatinib/Compound A and binimetinib in GIST-T1/D816E
binimetinib 0nM
binimetinib 500 nM
binimetinib 1000 nM
binimetinib 2000 nM
binimetinib 3000 nM
# of colonies (% of control)
120
100
80
60
40
20
0
Compound A 0nM
500nM Imatinib
Compound A 100nM
Compound A 250nM

Fig. 10C

GIST-T1/T670I



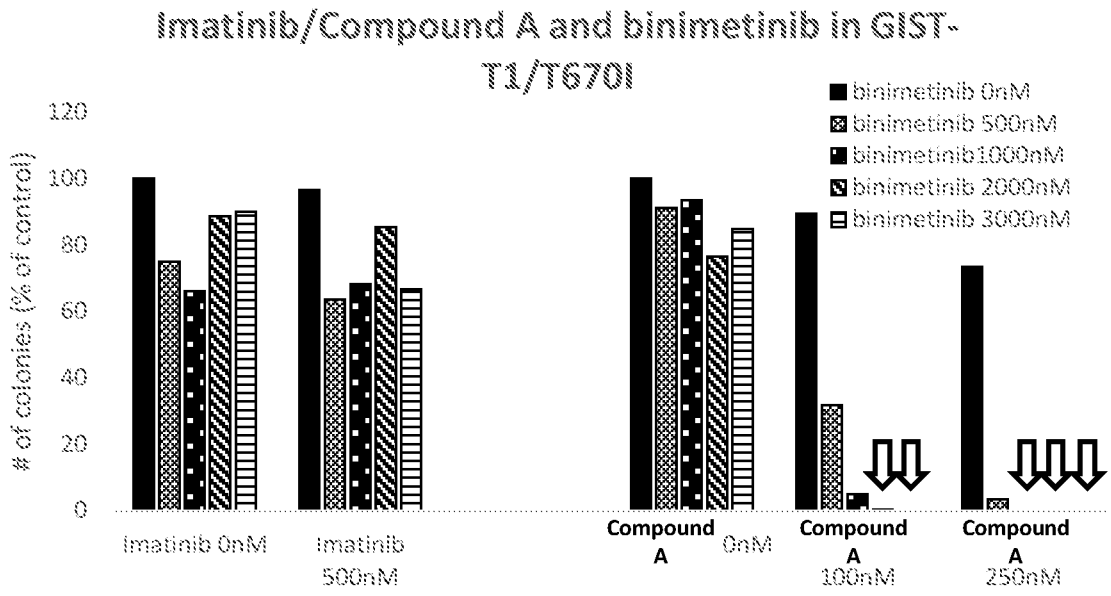
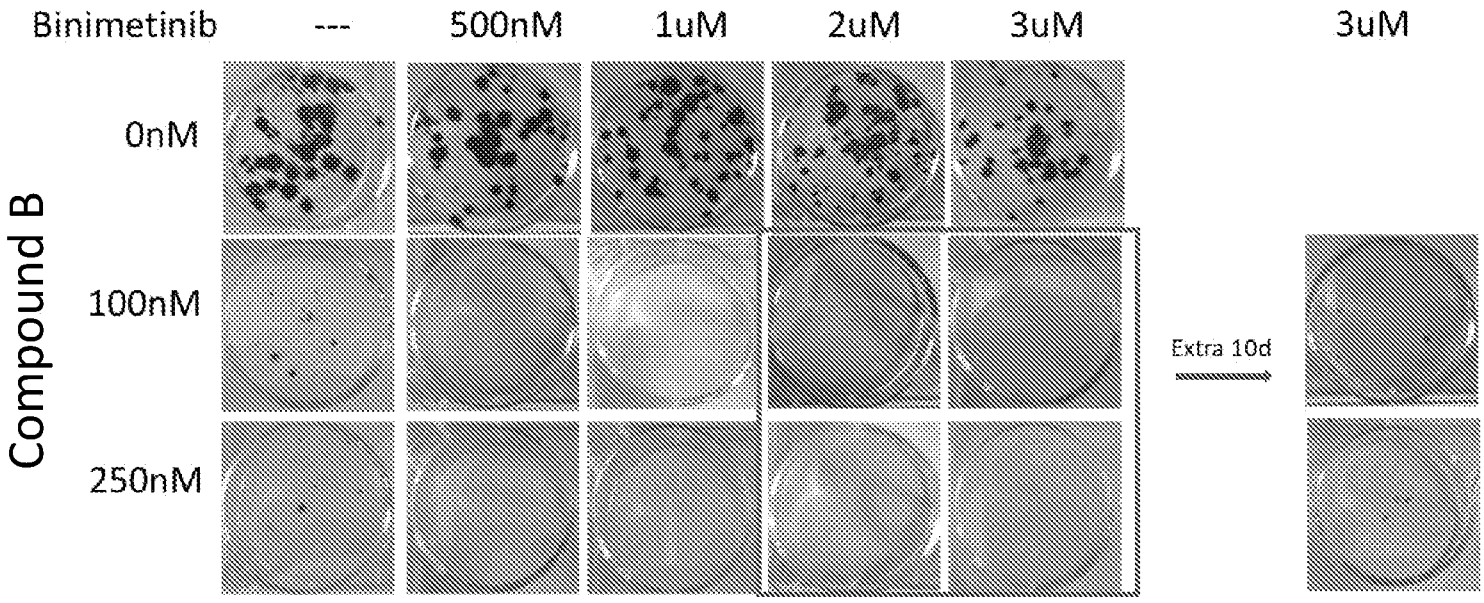


Fig. 11A


GIST-T1
Binimetinib

500nM
1uM
2uM
3uM
3uM
Compound B
0nM
100nM
250nM
Extra 10d

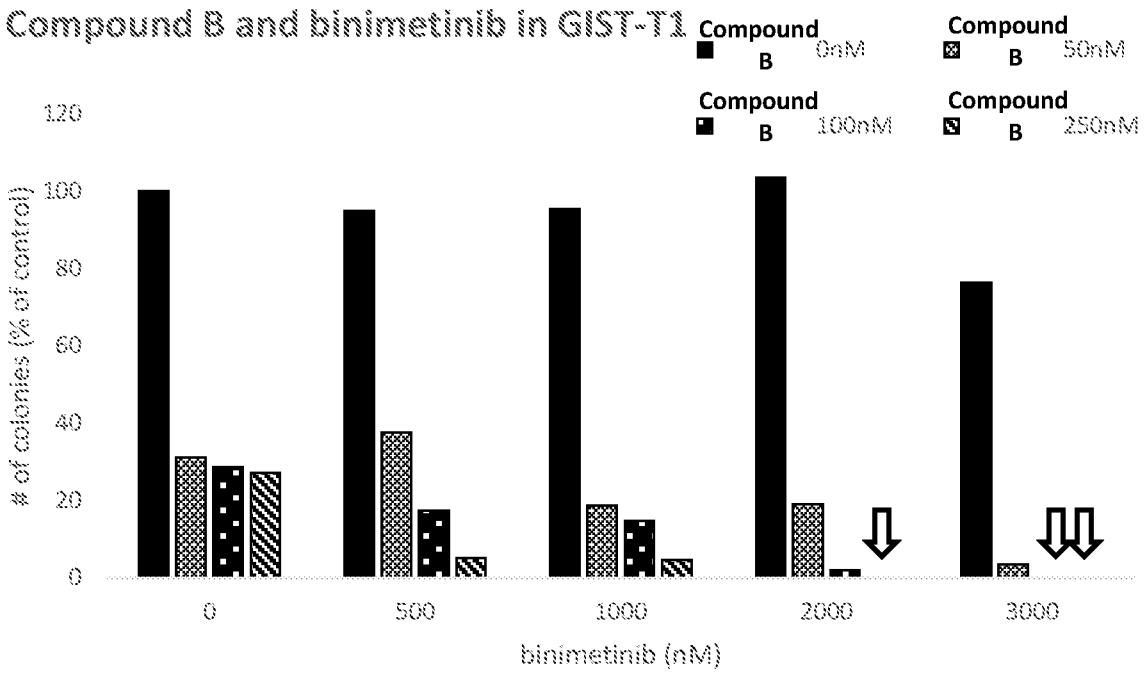
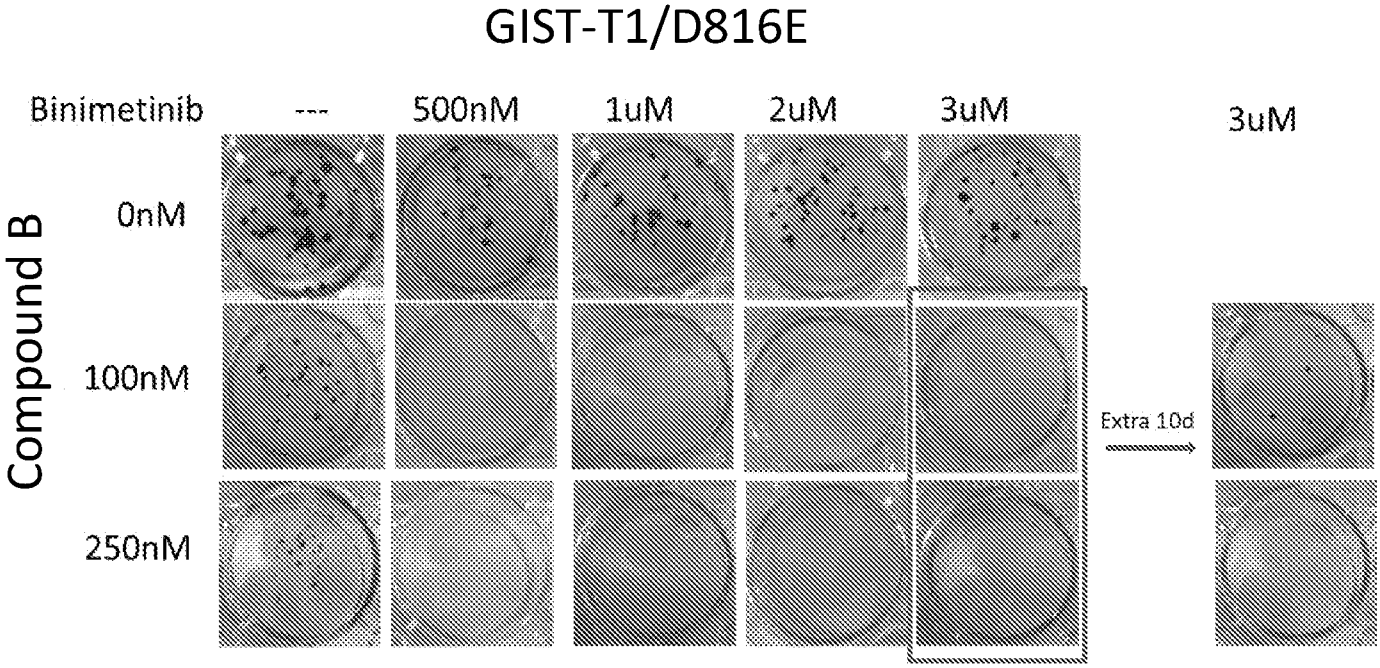

Compound B and binimetinib in GIST-T1
Compound B 0nM
Compound B 50nM
Compound B 100nM
Compound B 250nM
# of colonies (% of control)
120
100
80
60
40
20
0
0
500
1000
2000
3000
binimetinib (nM)

Fig. 11B


GIST-T1/D816E
Binimetinib

500nM
1uM
2uM
3uM
3uM
Compound B
0nM
100nM
250nM
Extra 10d

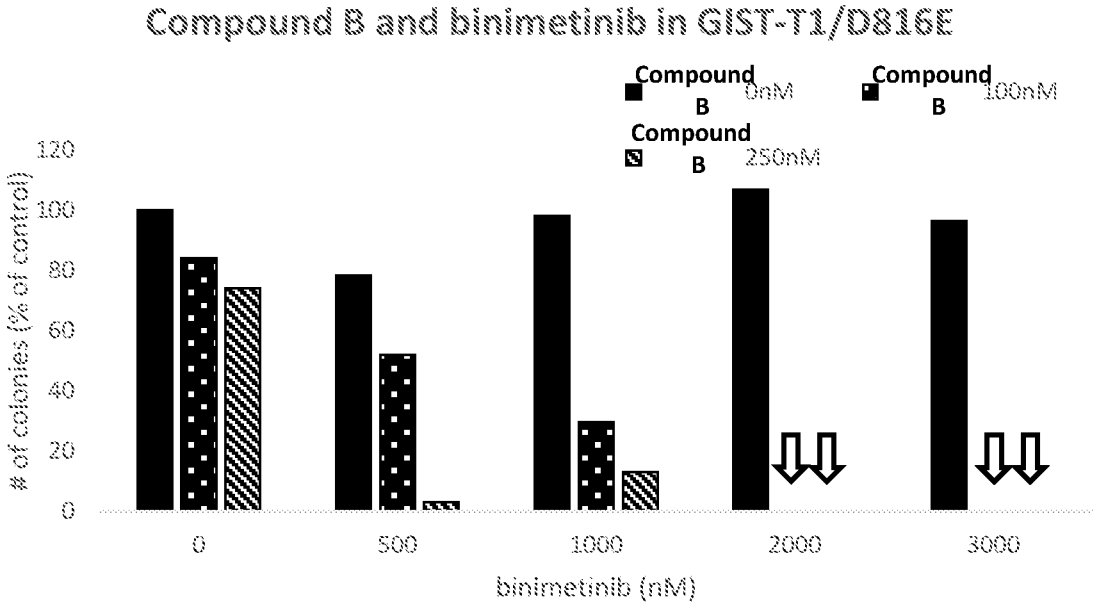
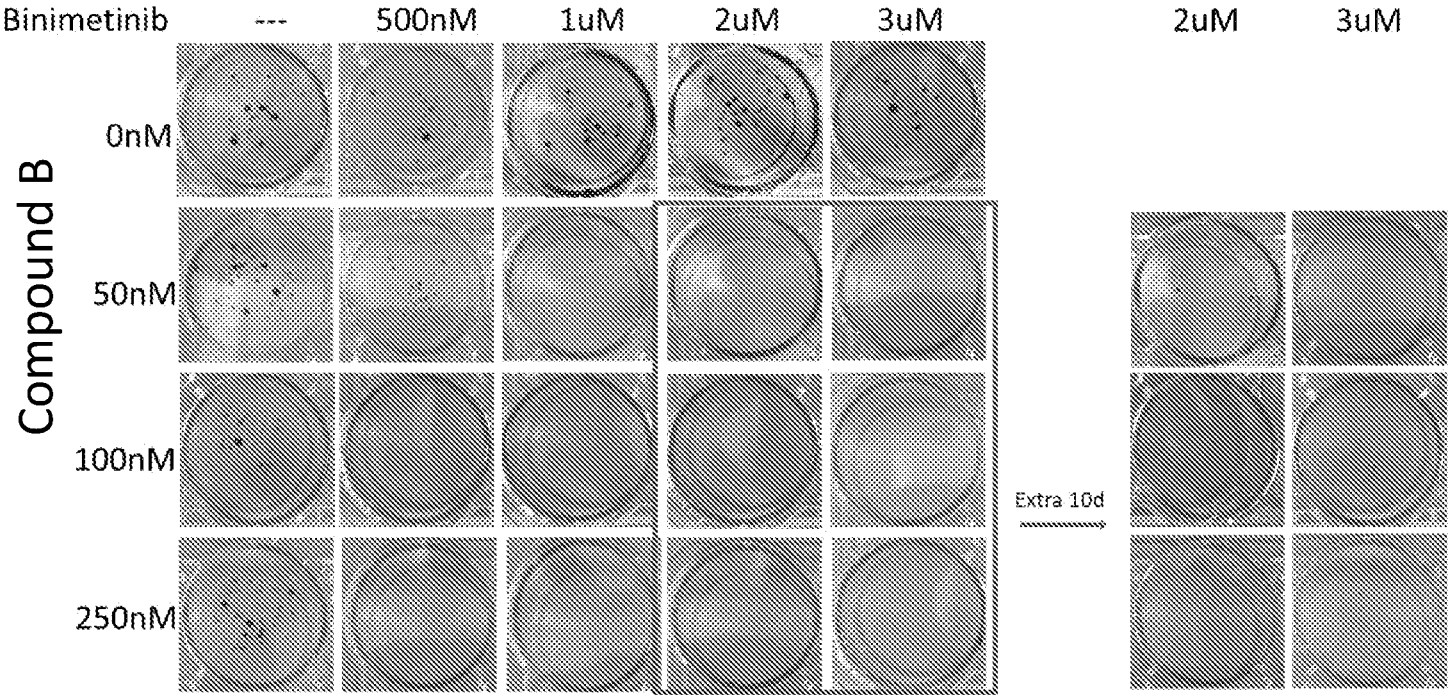

Compound B and binimetinib in GIST-T1/D816E
Compound B 0nM
Compound B 100nM
Compound B 250nM
# of colonies (% of control)
120
100
80
60
40
20
0
0
500
1000
2000
3000
binimetinib (nM)

Fig. 11C

GIST-T1/T670I



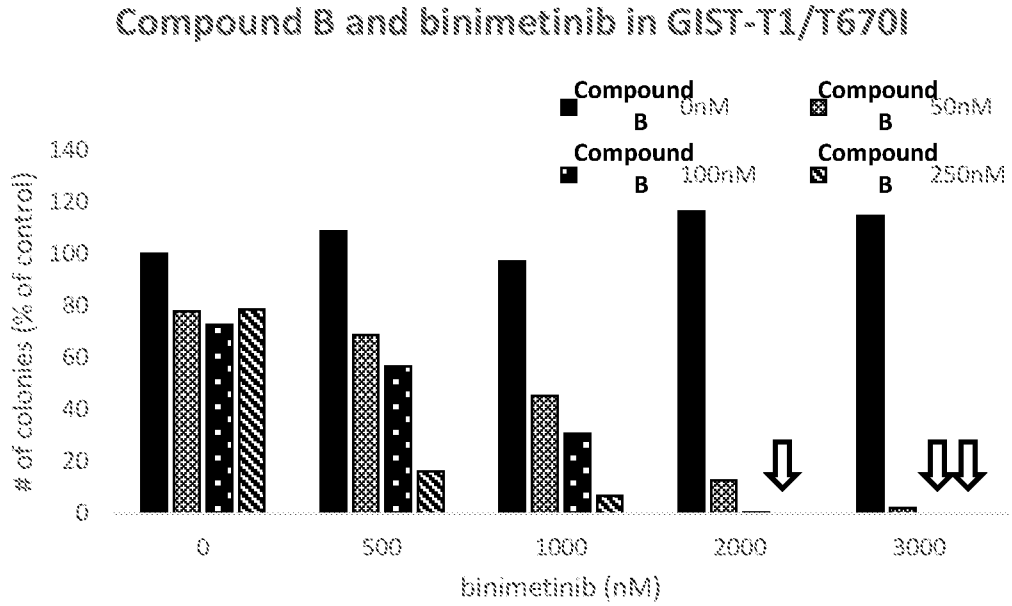
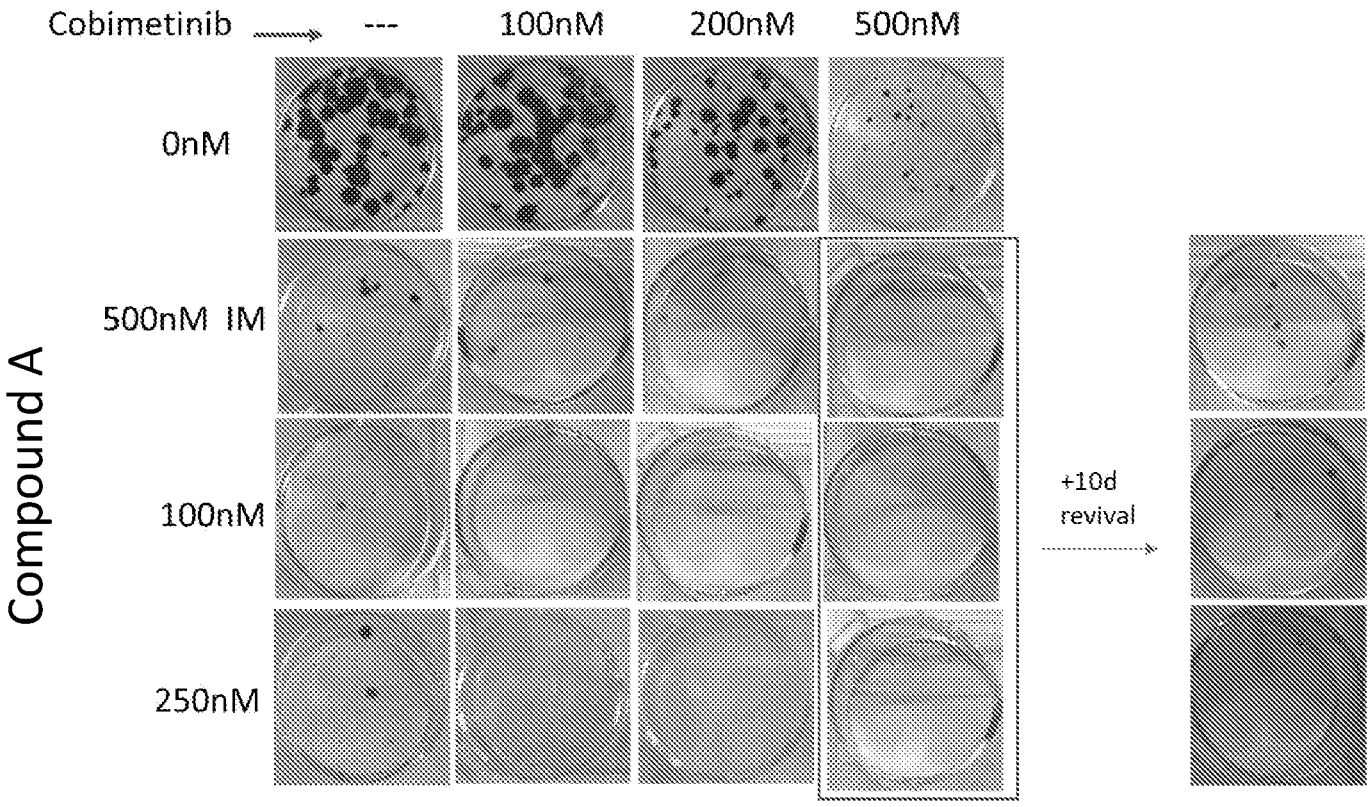


Fig. 12A

GIST-T1



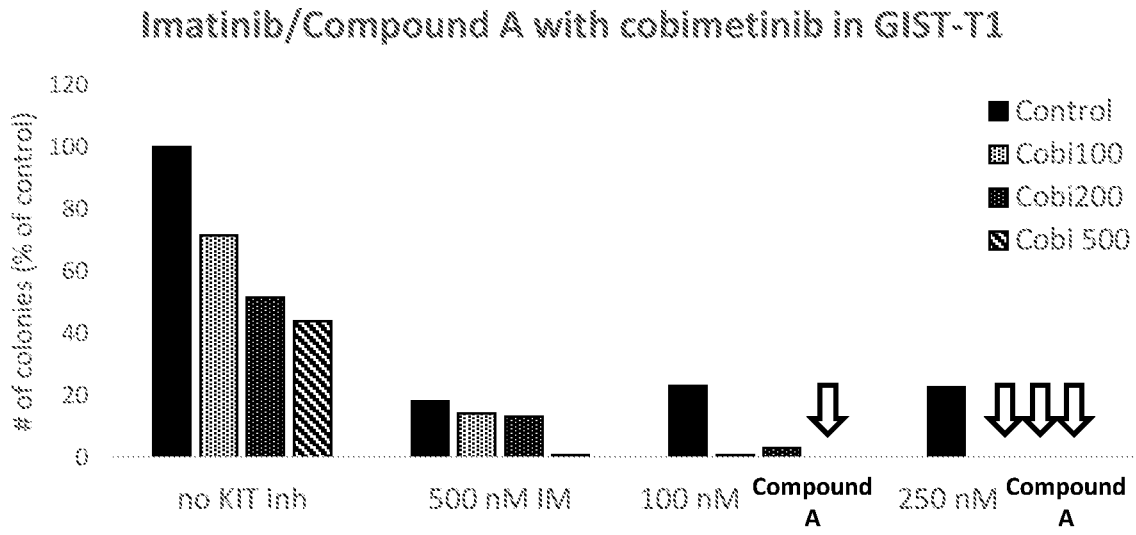
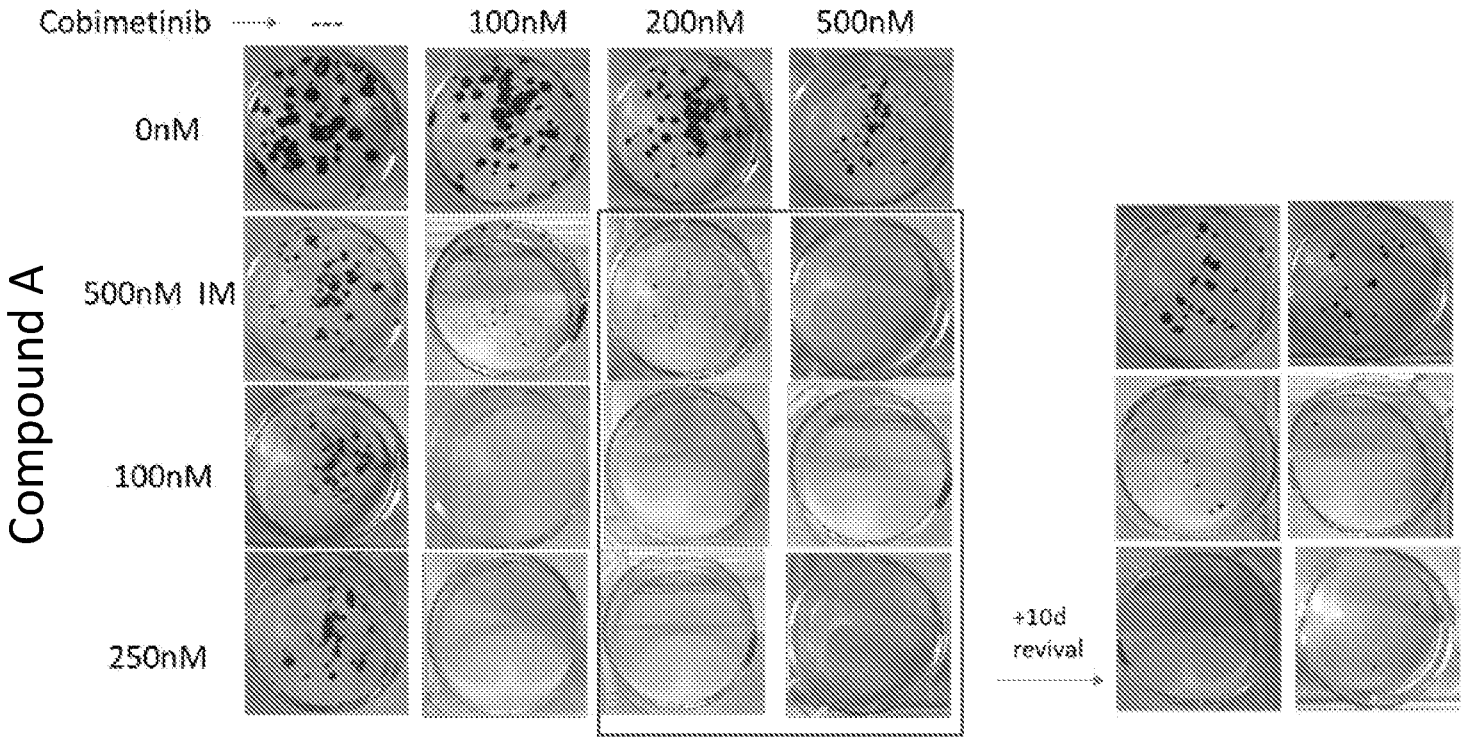


Fig. 12B


GIST-T1/D816E
Cobimetinib
100nM
200nM
500nM
0nM
500nM IM
100nM
250nM
Compound A
+10d
revival

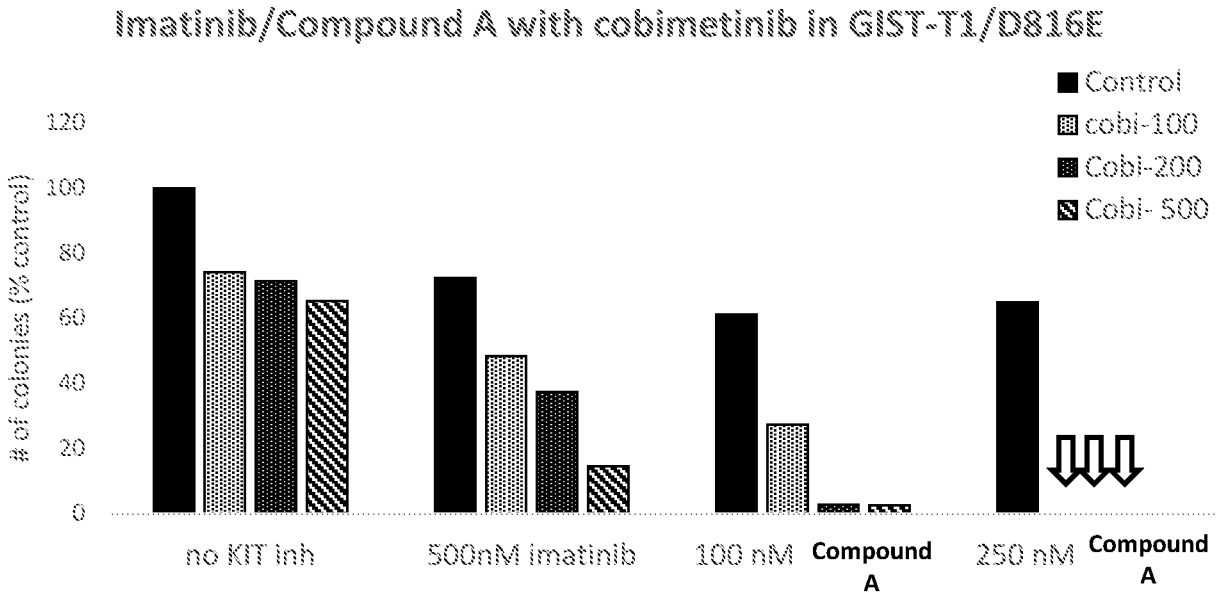
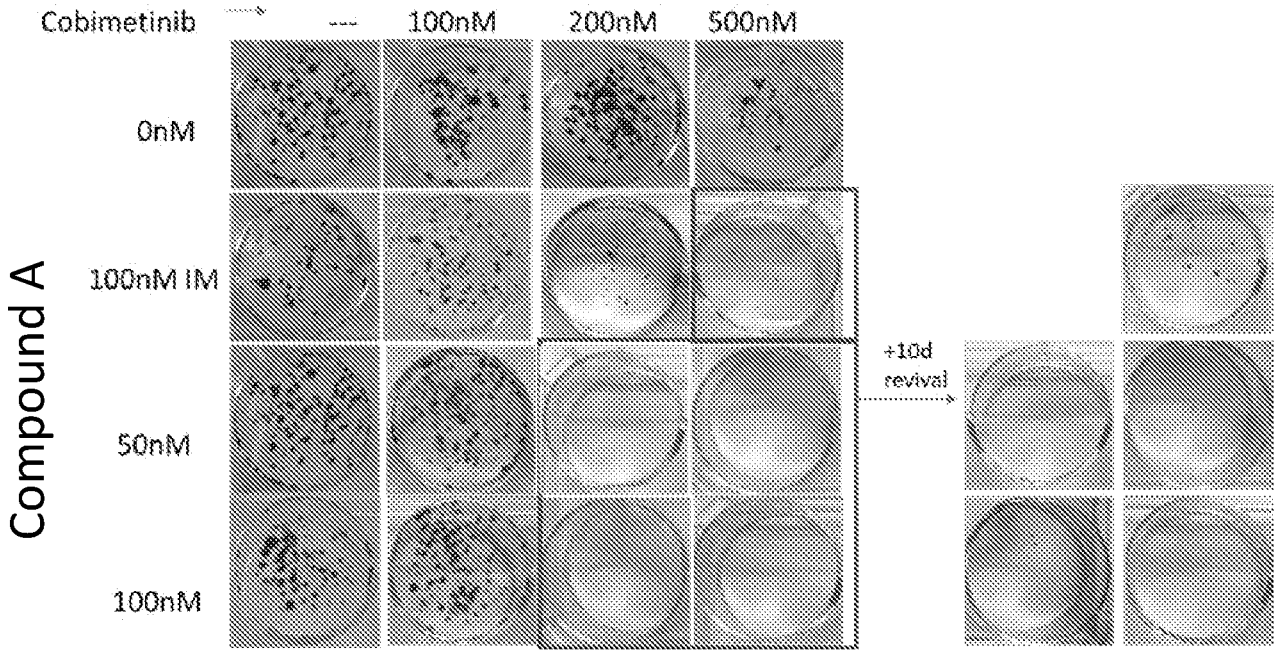

Imatinib/Compound A with cobimetinib in GIST-T1/D816E
Control
cobi-100
Cobi-200
Cobi- 500
# of colonies (% control)
120
100
80
60
40
20
0
no KIT inh
500nM imatinib
100 nM Compound A
250 nM Compound A

Fig. 12C

GIST-T1/T670I



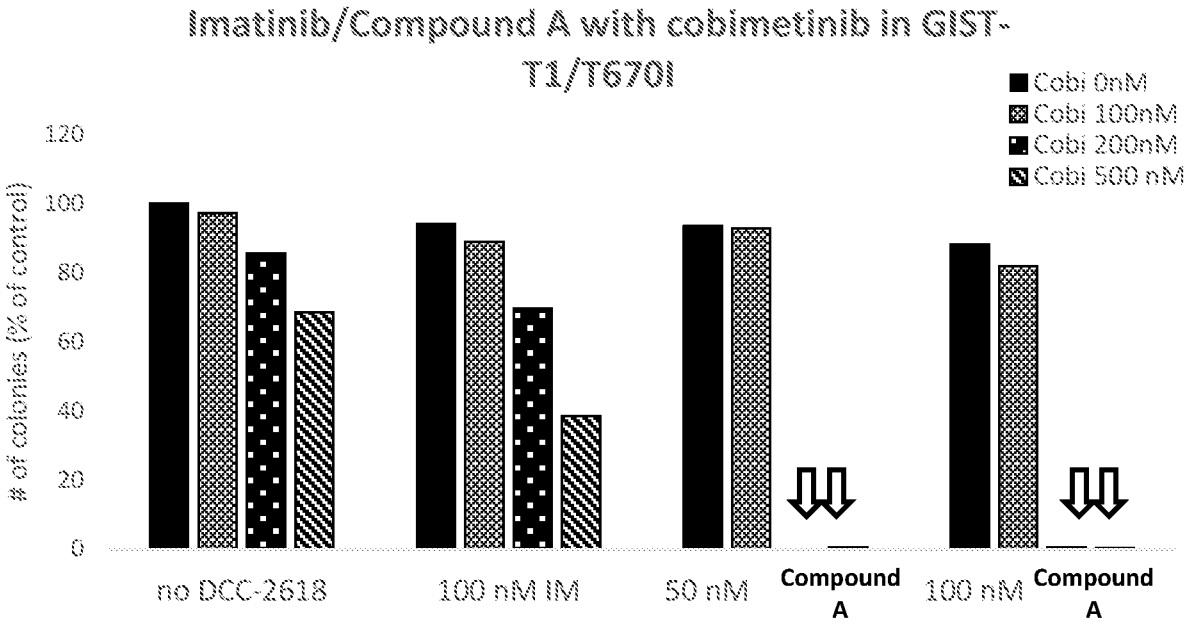


Fig. 13A

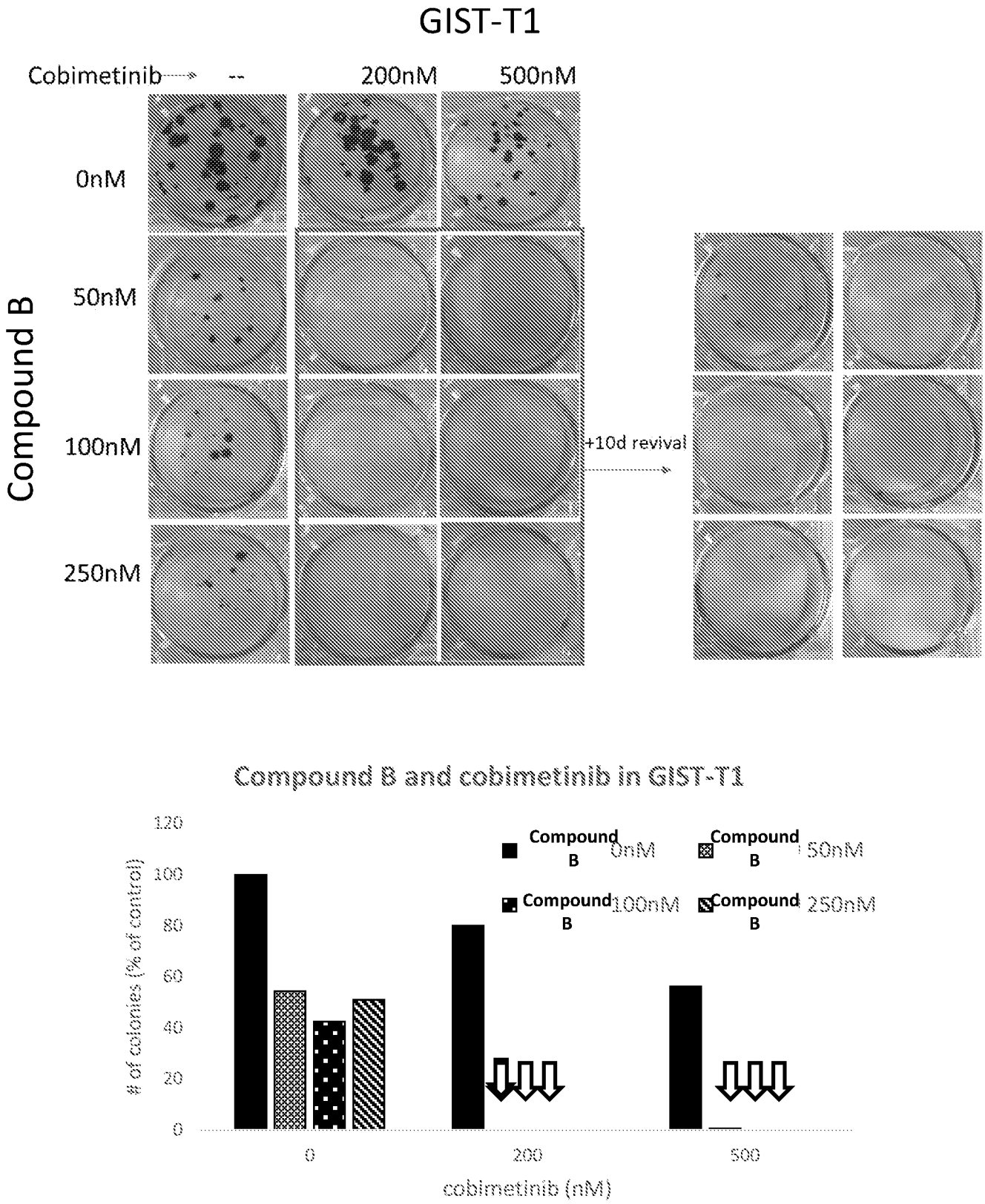
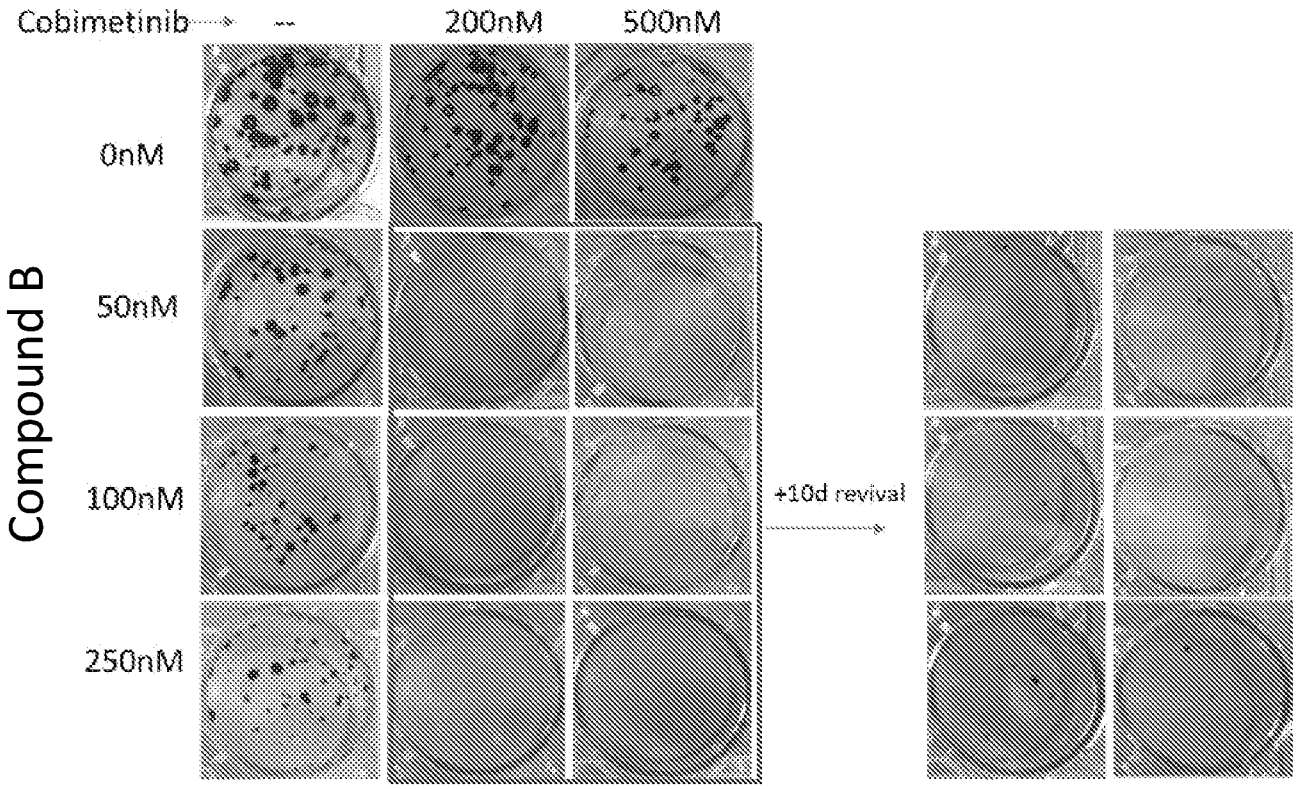

GIST-T1
Cobimetinib
--
200nM
500nM
0nM
50nM
100nM
250nM
Compound B
+10d revival
Compound B and cobimetinib in GIST-T1
# of colonies (% of control)
120
100
80
60
40
20
0
Compound B 0nM
Compound B 50nM
Compound B 100nM
Compound B 250nM
0
200
500
cobimetinib (nM)

Fig. 13B

GIST-T1/D816E



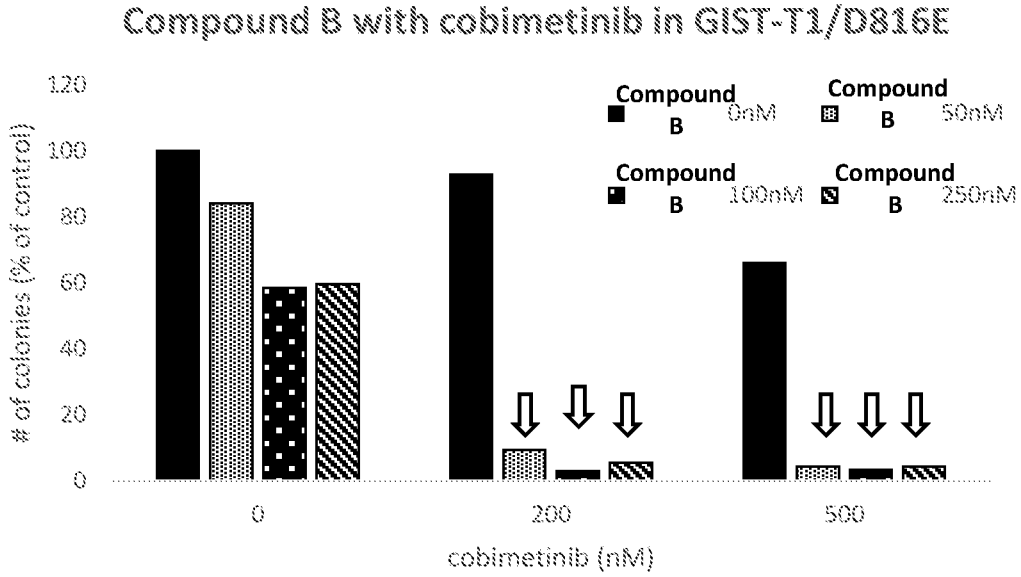


Fig. 13C

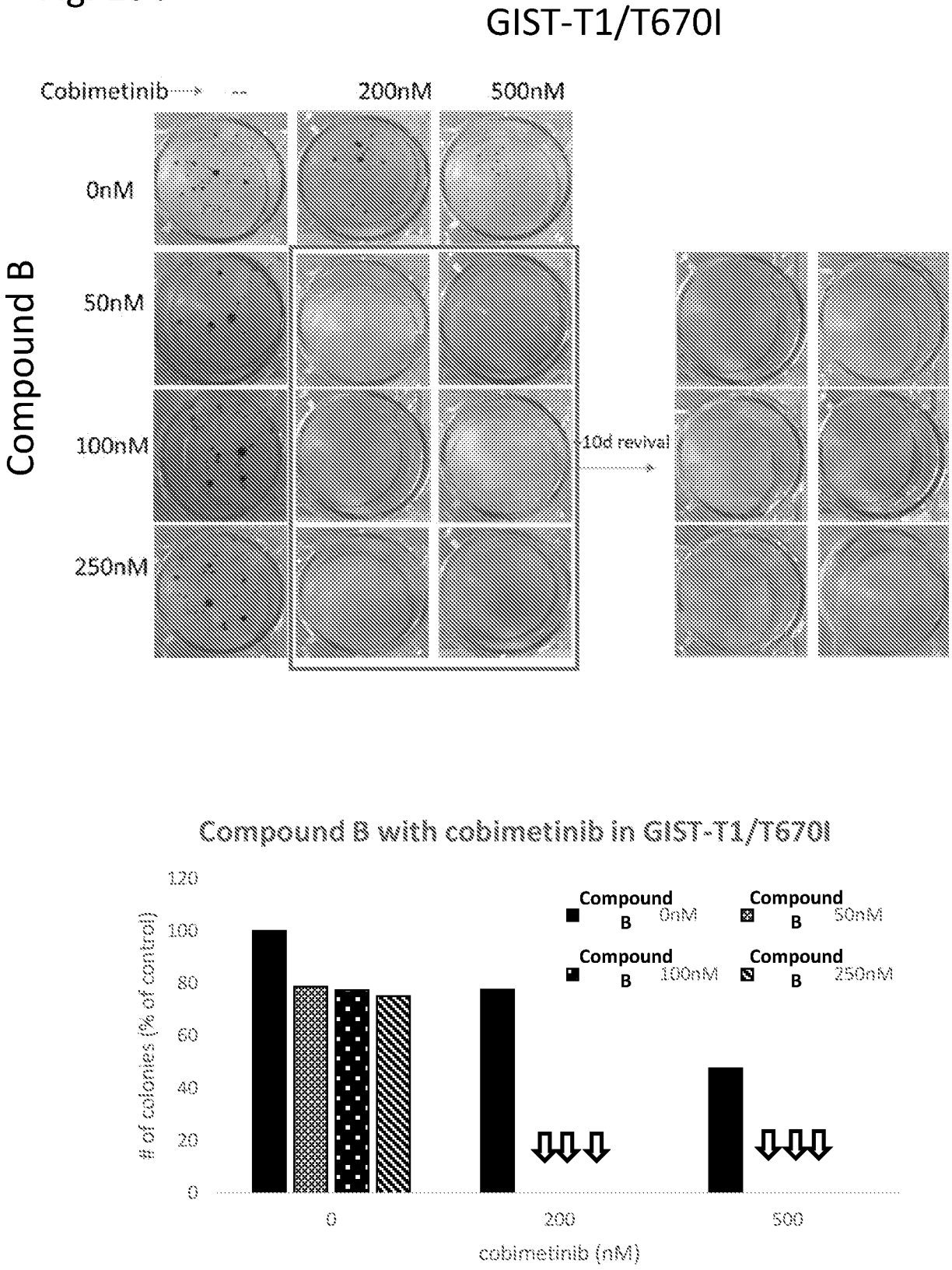
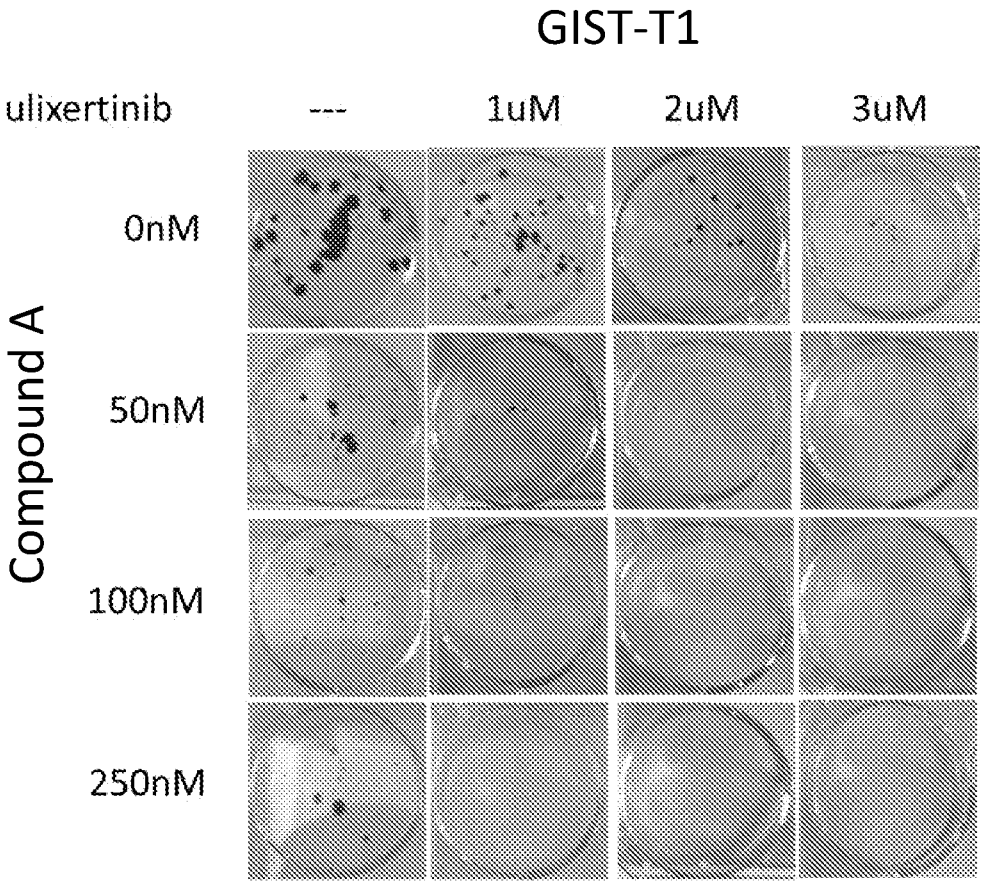

GIST-T1/T670I
Cobimetinib
0nM
200nM
500nM
Compound B
0nM
50nM
100nM
250nM
10d revival
Compound B with cobimetinib in GIST-T1/T670I
# of colonies (% of control)
120
100
80
60
40
20
0
Compound B 0nM
Compound B 50nM
Compound B 100nM
Compound B 250nM
0
200
500
cobimetinib (nM)

Fig. 14A


GIST-T1
ulixertinib

1uM
2uM
3uM
Compound A
0nM
50nM
100nM
250nM

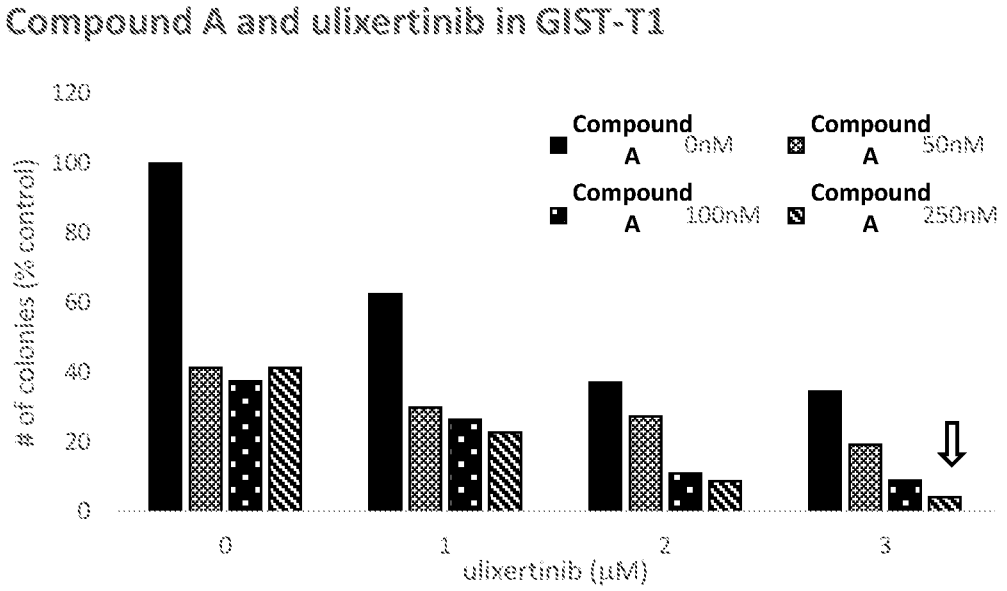
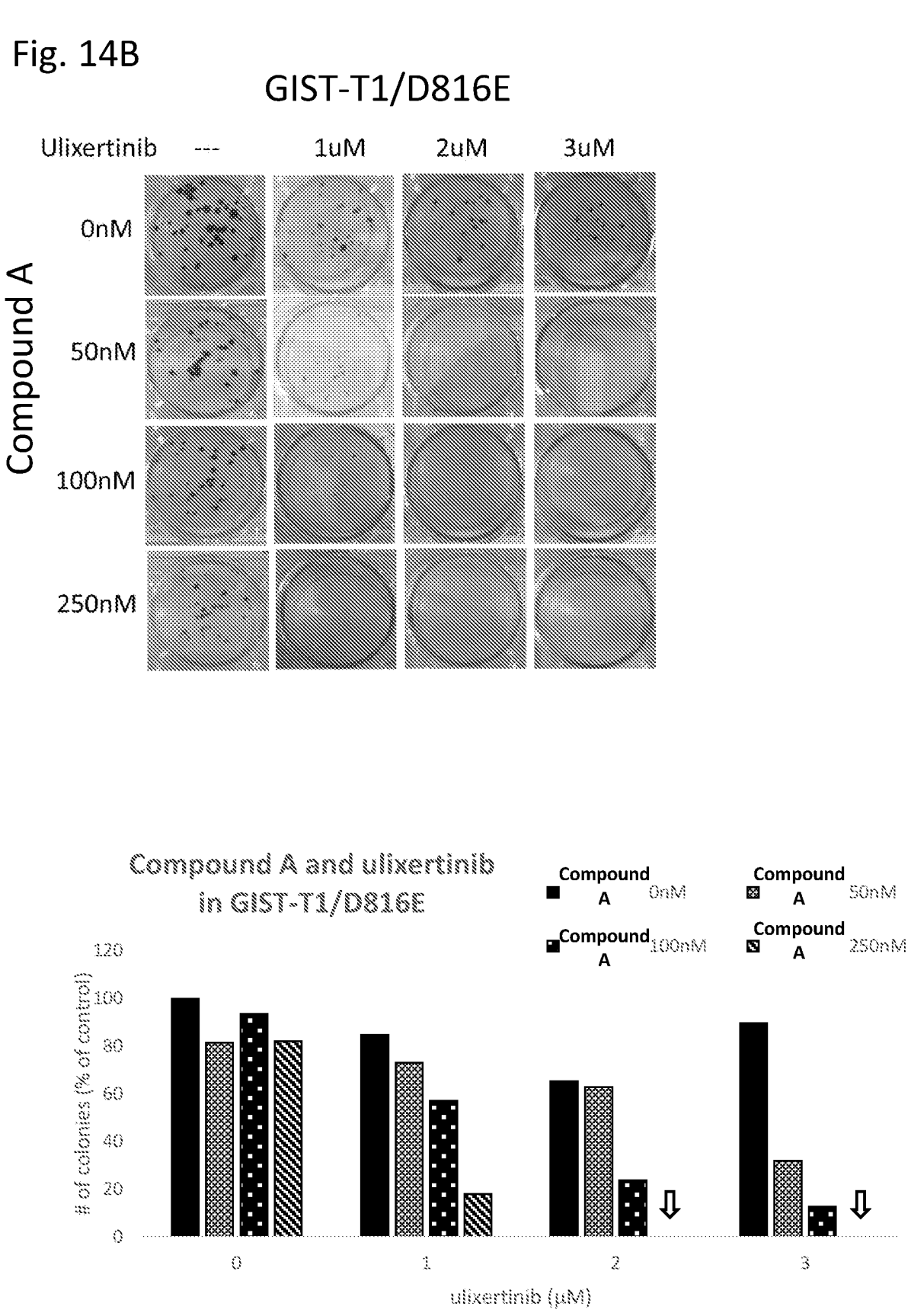
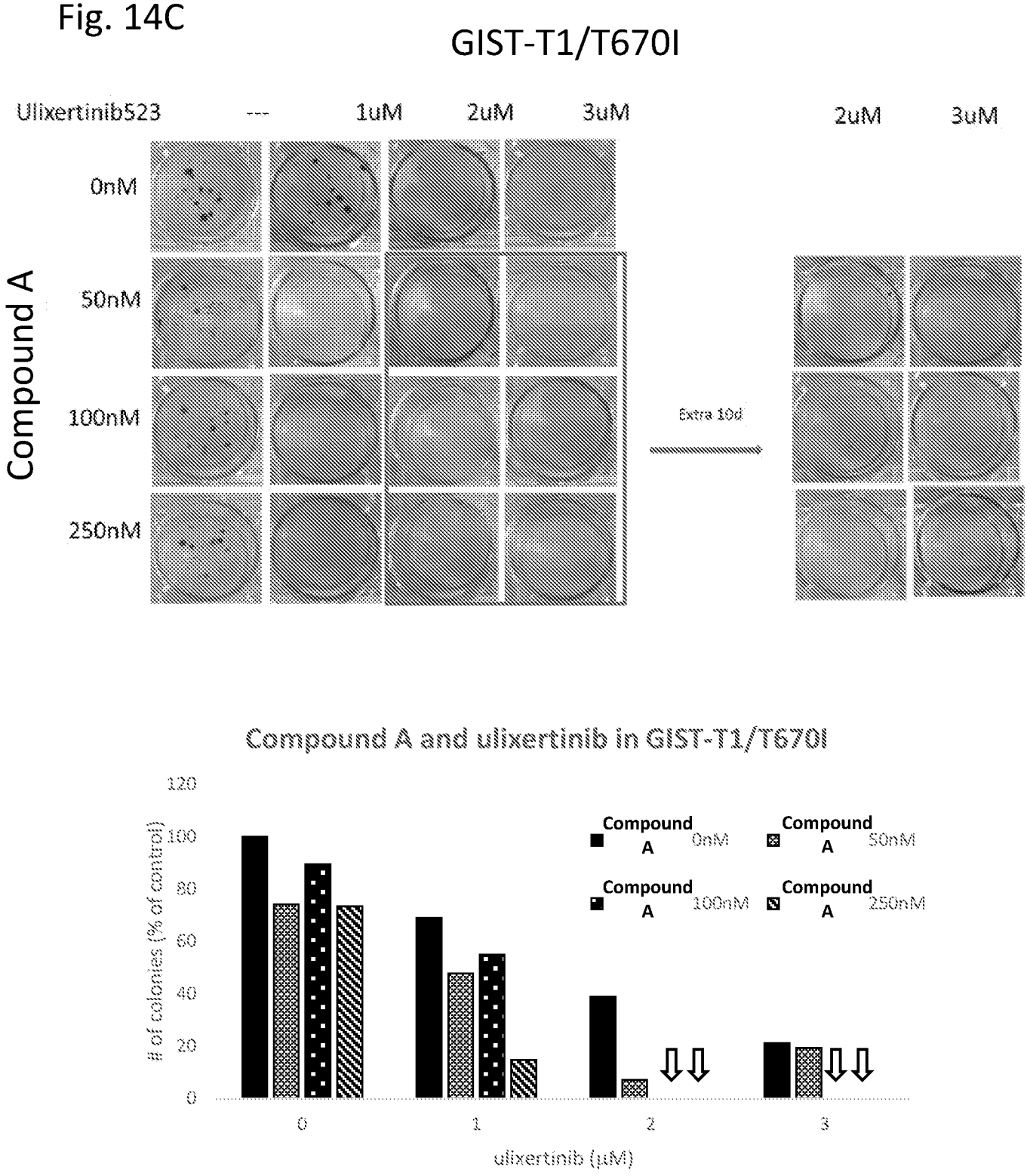

Compound A and ulixertinib in GIST-T1
# of colonies (% control)
120
100
80
60
40
20
0
0
1
2
3
ulixertinib (μM)
Compound A 0nM
Compound A 50nM
Compound A 100nM
Compound A 250nM

Fig. 14B


GIST-T1/D816E
Ulixertinib

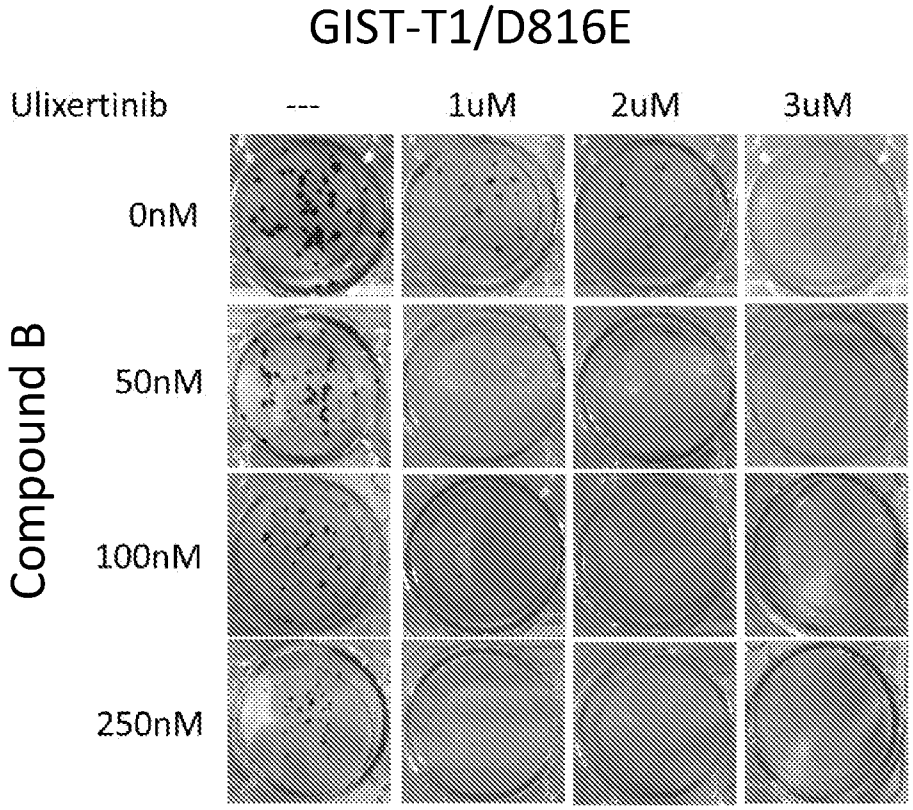
1uM
2uM
3uM
Compound A
0nM
50nM
100nM
250nM
Compound A and ulixertinib in GIST-T1/D816E
Compound A 0nM
Compound A 50nM
Compound A 100nM
Compound A 250nM
# of colonies (% of control)
120
100
80
60
40
20
0
0
1
2
3
ulixertinib (μM)

Fig. 14C


GIST-T1/T670I
Ulixertinib523

1uM
2uM
3uM
2uM
3uM
Compound A
0nM
50nM
100nM
250nM
Extra 10d
Compound A and ulixertinib in GIST-T1/T670I
# of colonies (% of control)
120
100
80
60
40
20
0
Compound A 0nM
Compound A 50nM
Compound A 100nM
Compound A 250nM
0
1
2
3
ulixertinib (μM)

Fig. 15


GIST-T1/D816E
Ulixertinib

1uM
2uM
3uM
Compound B
0nM
50nM
100nM
250nM

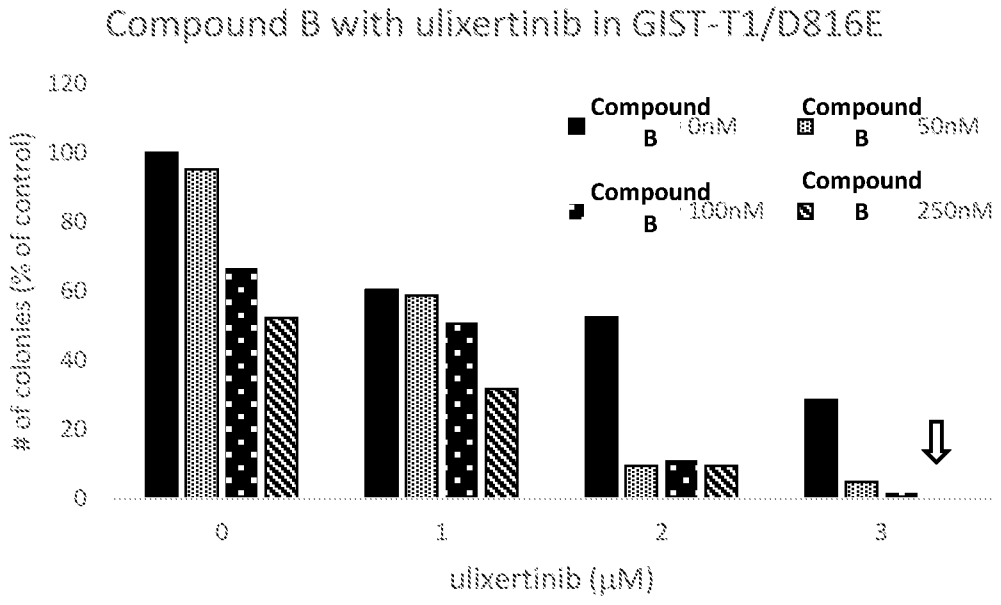

Compound B with ulixertinib in GIST-T1/D816E
# of colonies (% of control)
120
100
80
60
40
20
0
Compound B 0nM
Compound B 50nM
Compound B 100nM
Compound B 250nM
0
1
2
3
ulixertinib (μM)

FIG. 16A

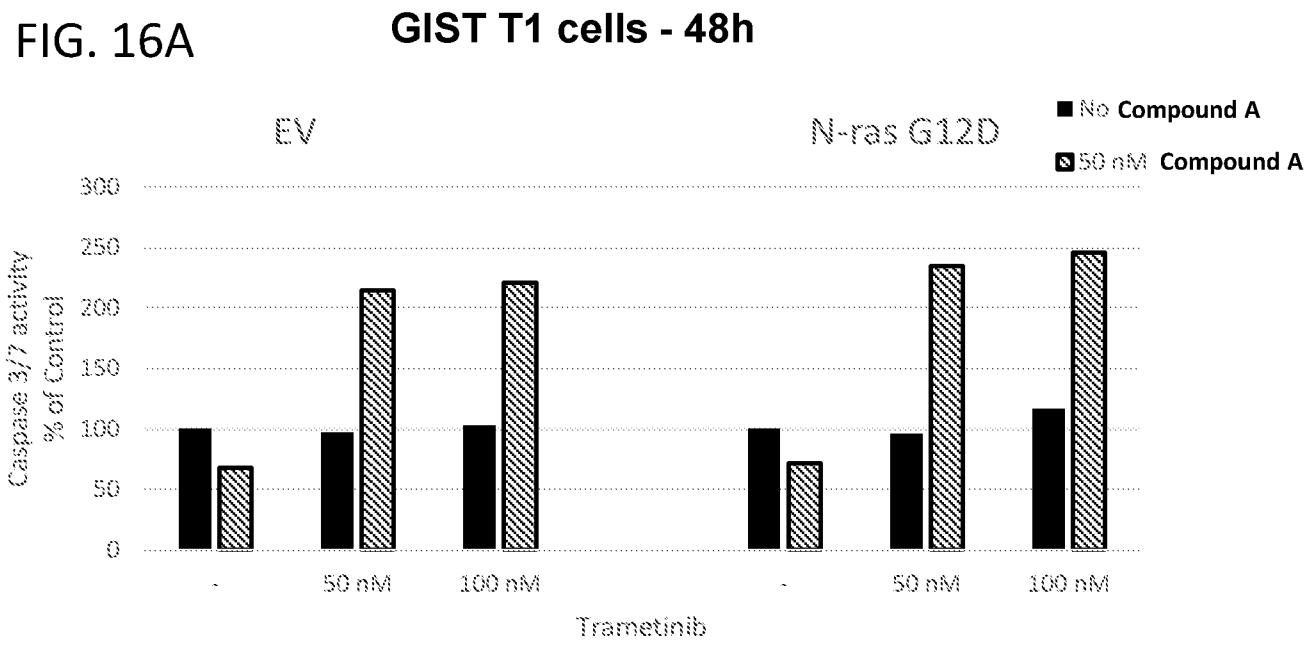


FIG. 16B.1

FIG. 16B.2

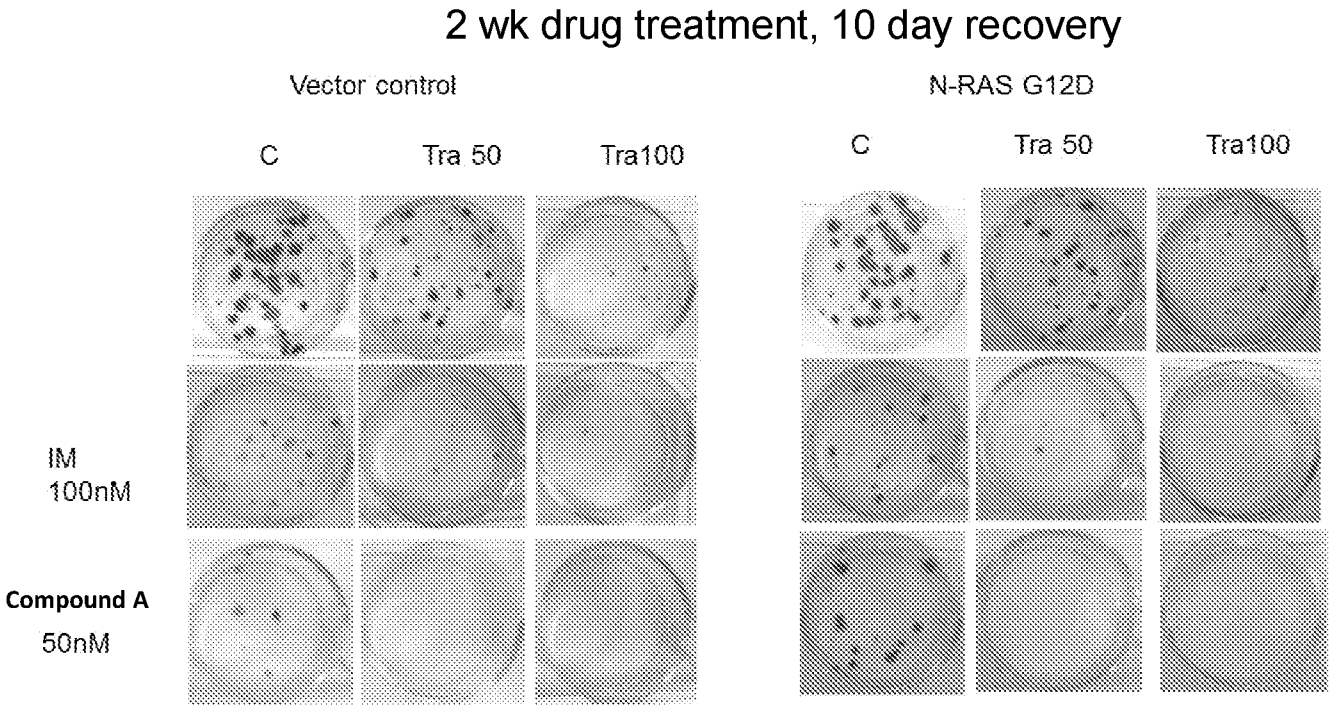


FIG. 16C.1

FIG. 16C.2

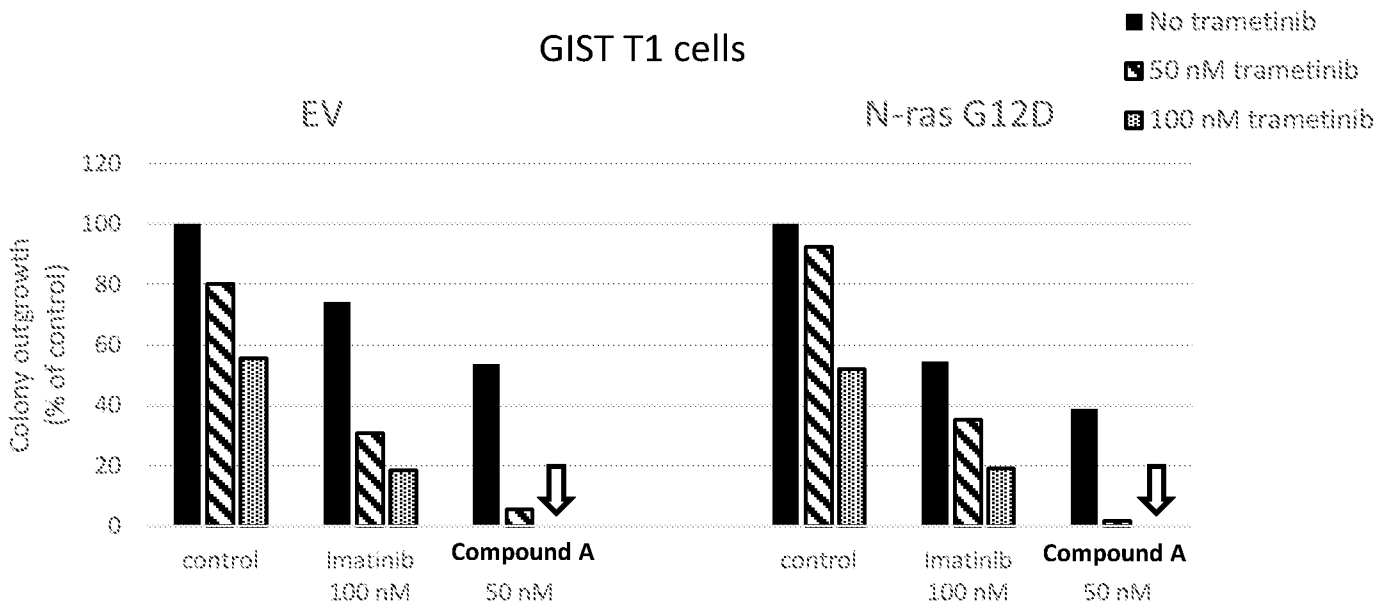


FIG. 16D

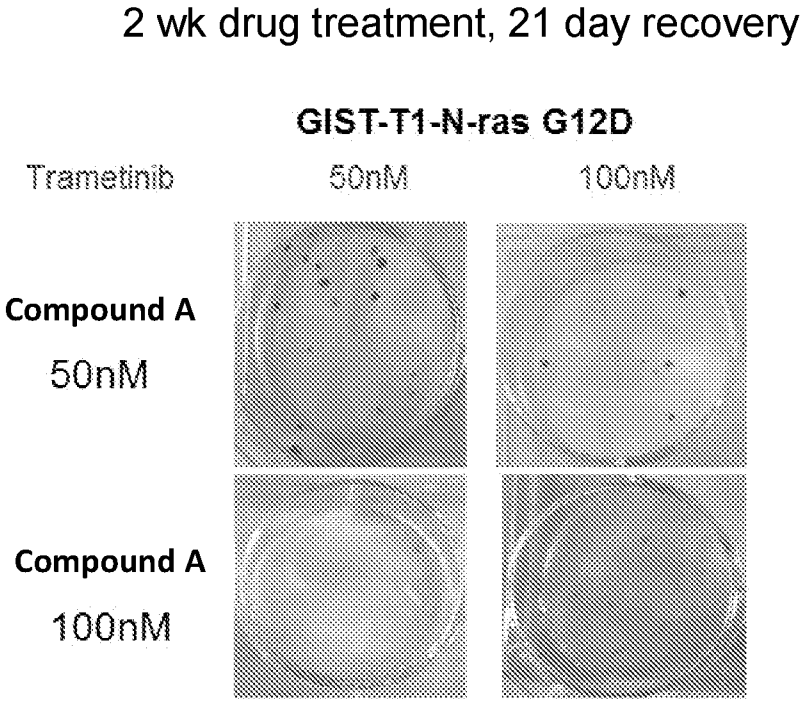
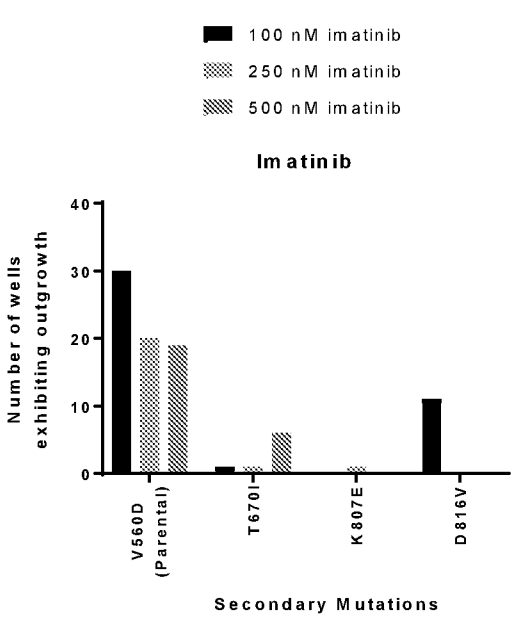


FIG. 17A



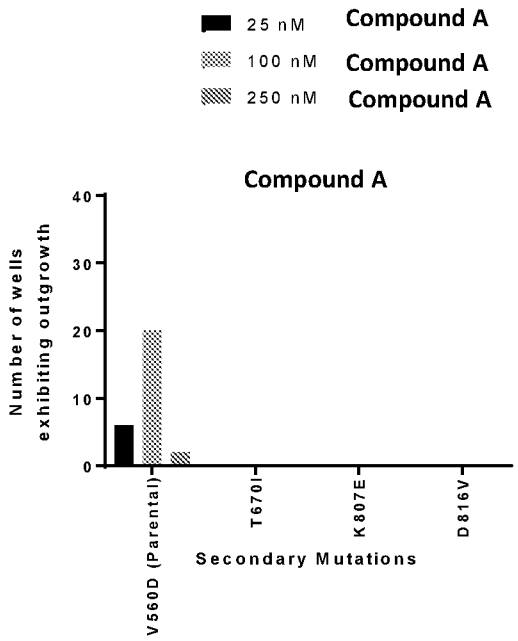
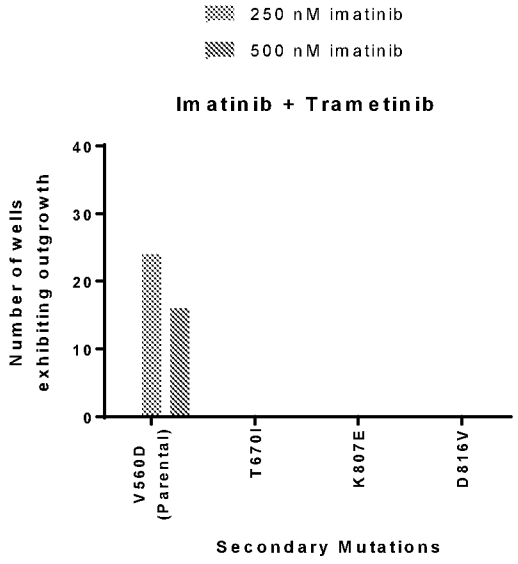


FIG. 17B



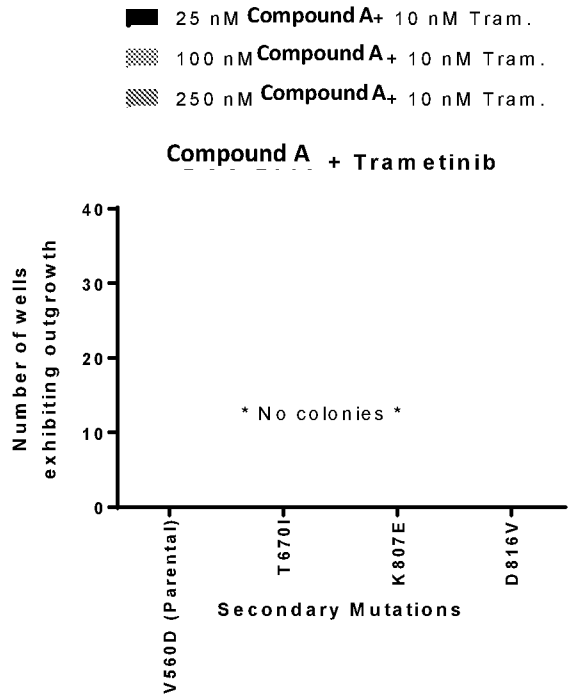


FIG. 18A

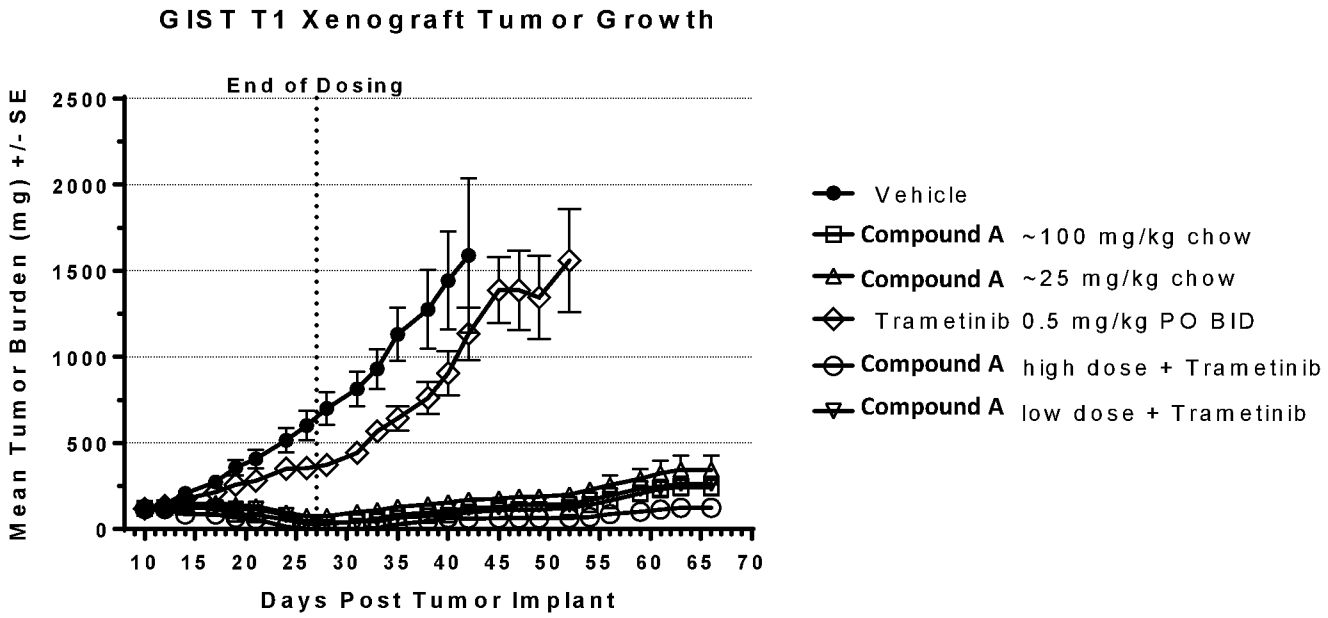


FIG. 18B

