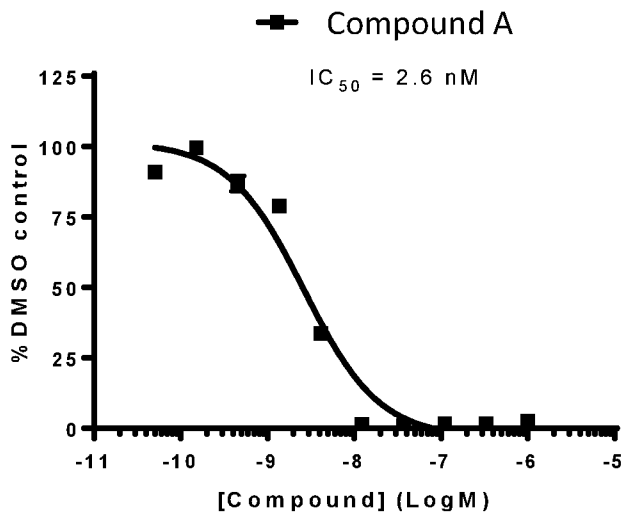
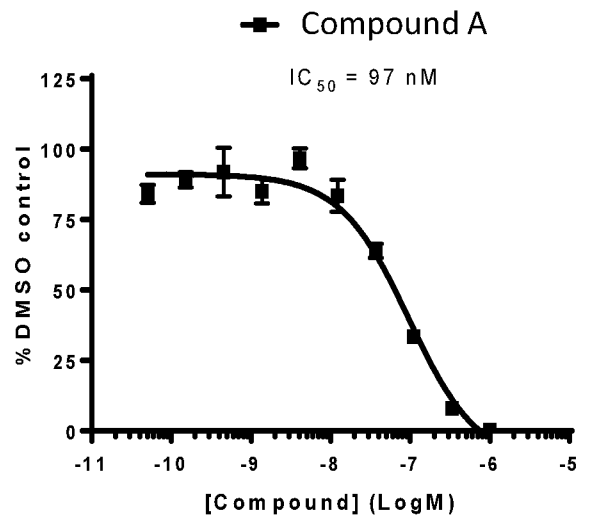


Figure 1A

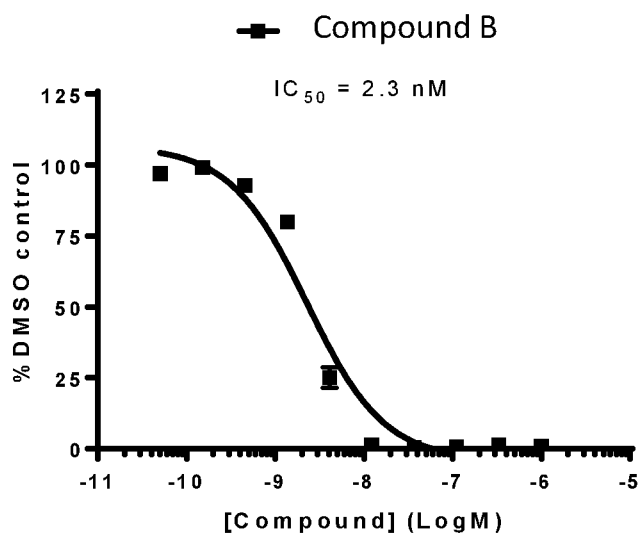


HMC1.1 V560G

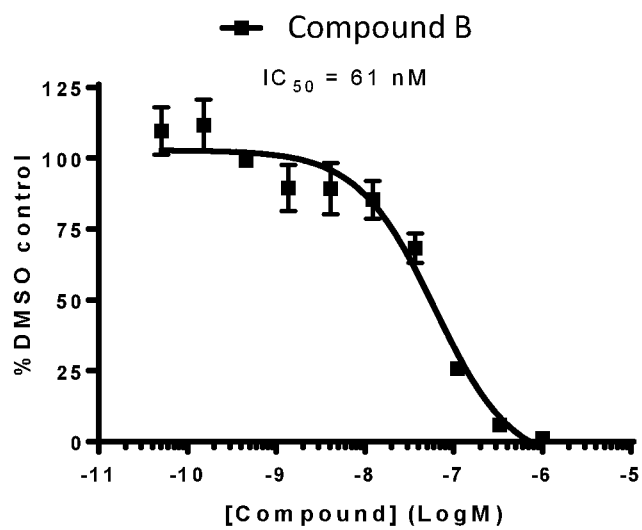


HMC1.1 V560G/D816V

Figure 1B



HMC1.1 V560G



HMC1.1 V560G/D816V

Figure 2A

Compound A and trametinib combination in HMC1.2 cells

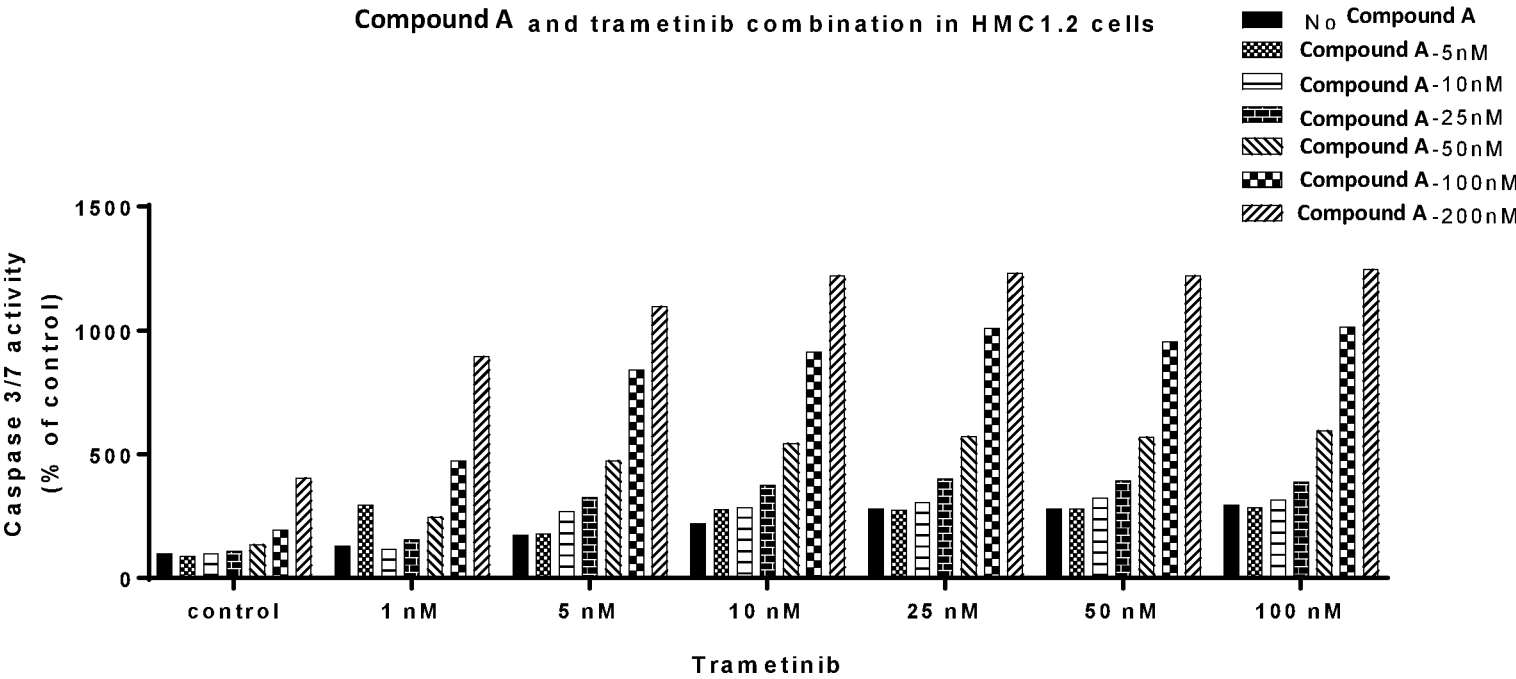


Figure 2B

COMBO Index	Compound A 5nM	Compound A 10nM	Compound A 25nM	Compound A 50nM	Compound A 100nM	Compound A 200nM
Trametinib 1nM	0.03993	2.64367	6.01481	0.44649	0.11076	0.01411
Trametinib 5nM	1.25589	0.19588	0.13256	0.05909	0.0101	0.00315
Trametinib 10nM	0.24985	0.23826	0.09809	0.03722	0.0063	9.34E-04
Trametinib 25nM	0.63422	0.36434	0.10901	0.03338	0.0032	8.28E-04
Trametinib 50nM	1.10038	0.48744	0.18814	0.03977	0.00477	9.35E-04
Trametinib 100nM	1.87791	1.06924	0.35501	0.04047	0.00308	6.93E-04

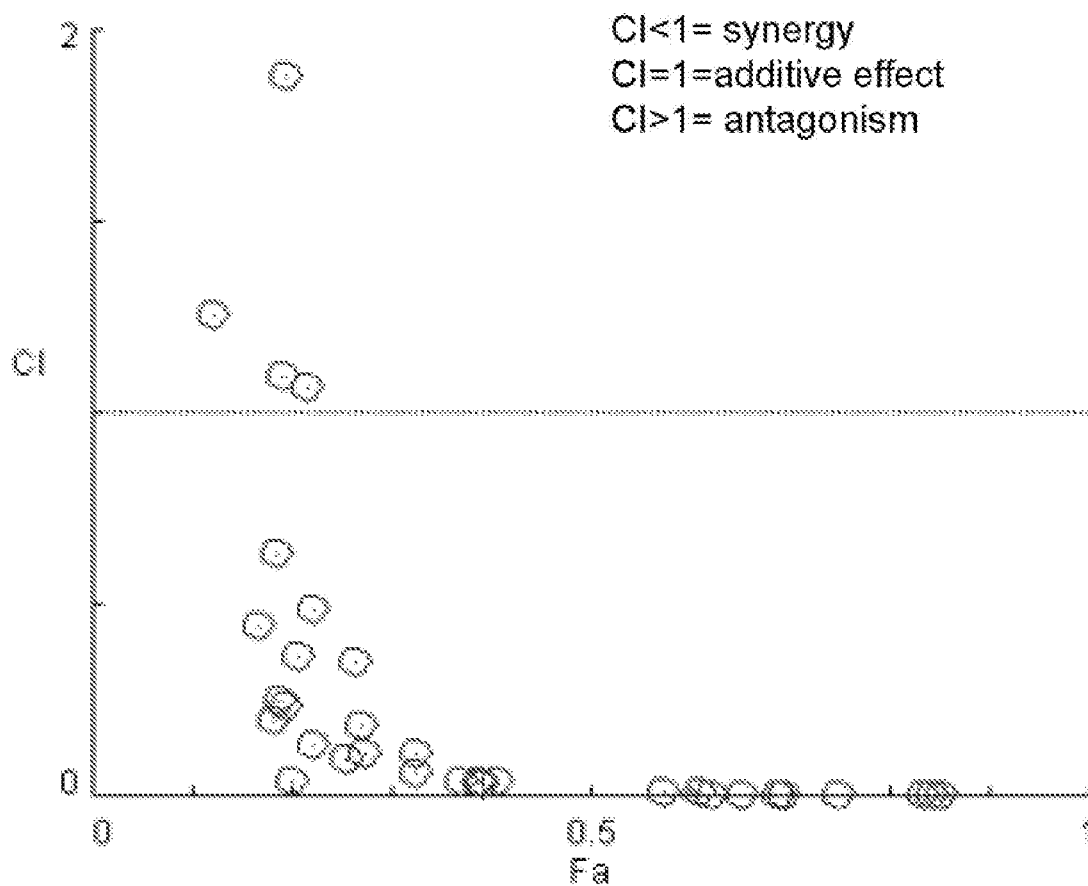
Figure 2C**Combination Index Plot**

Figure 3A

Compound B and trametinib combination in HMC1.2 cells

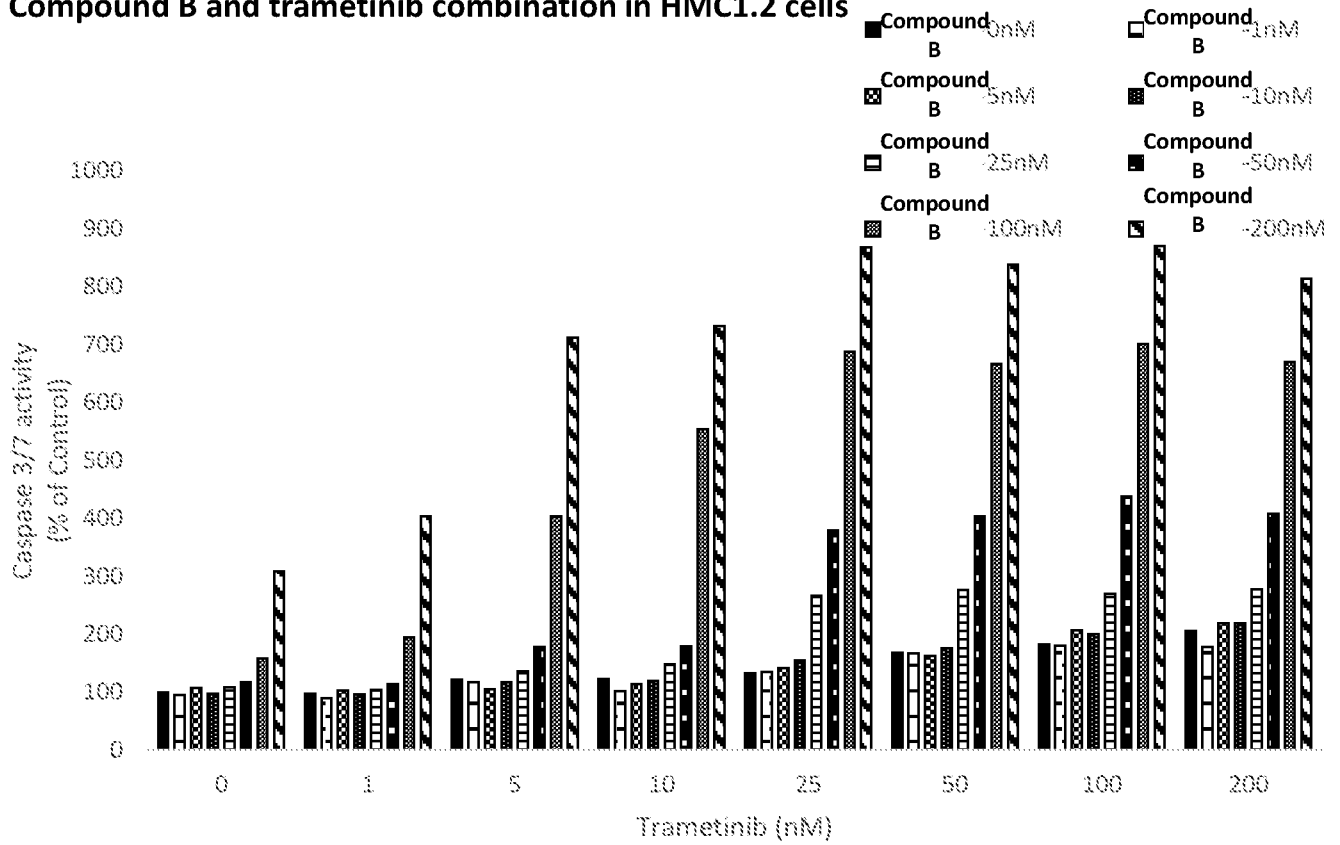


Figure 3B

Cl	Compound B 1nM	Compound B 5nM	Compound B 10nM	Compound B 25nM	Compound B 50nM	Compound B 100nM	Compound B 200nM
Trametinib 1nM	1.68069	1.40334	3.41889	5.07162	5.64363	0.57337	0.00964
Trametinib 5nM	1.05523	2.96535	1.86572	1.4174	0.53113	0.00478	2.29E-05
Trametinib 10nM	5.38596	3.16063	2.68309	1.06576	0.56445	2.84E-04	1.44E-05
Trametinib 25 nM	1.94547	1.57549	0.96476	0.03258	0.00435	1.97E-05	2.51E-07
Trametinib 50 nM	0.85054	1.07585	0.6726	0.0344	0.00289	3.12E-05	7.64E-07
Trametinib 100 nM	0.97626	0.35944	0.48969	0.06284	0.00169	1.52E-05	2.14E-07
Trametinib 200 nM	2.11003	0.45464	0.48568	0.08116	0.00419	3.14E-05	1.63E-06

Figure 3C

Combination index plot

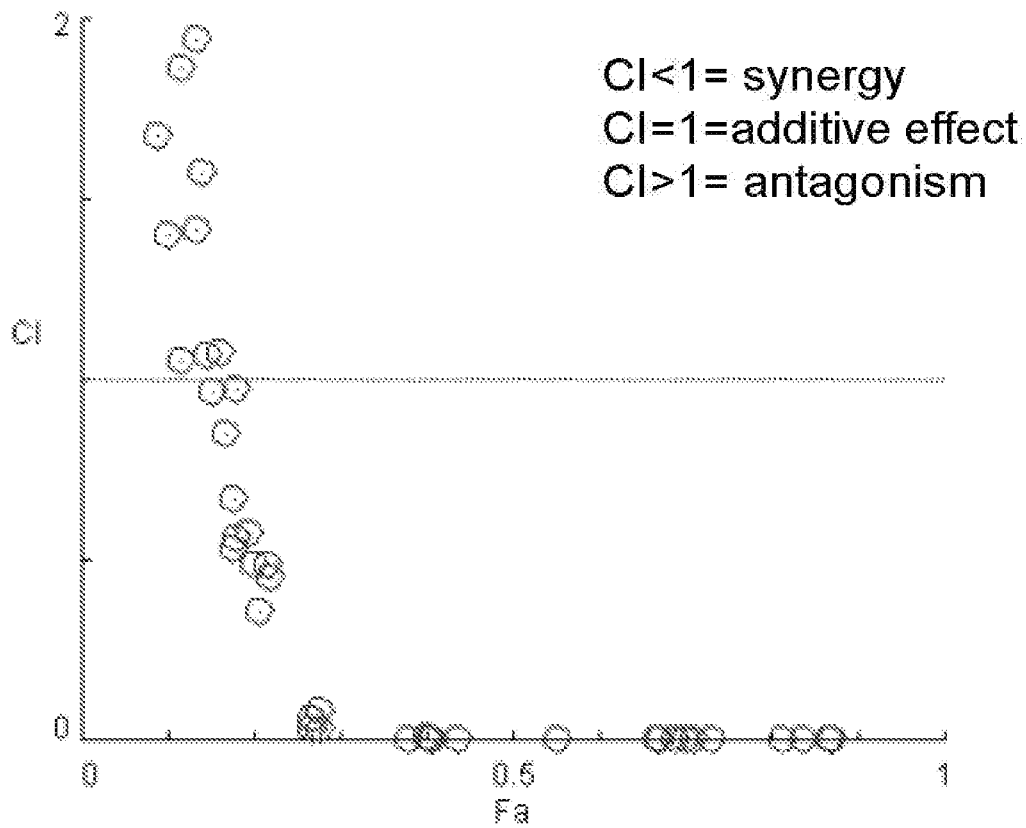


Figure 4A

Compound A and binimetinib combination in HMC1.2 cells

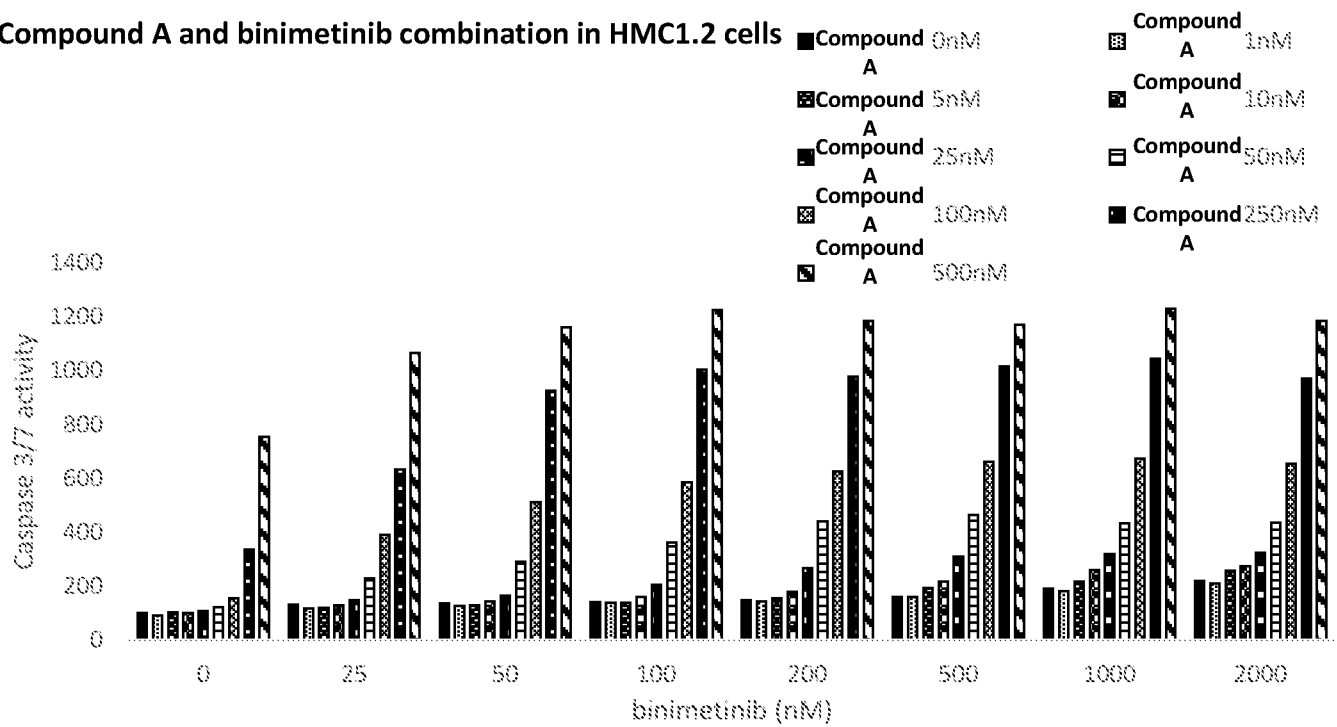


Figure 4B

Cl	Compound A 0nM	Compound A 5nM	Compound A 10nM	Compound A 25nM	Compound A 50nM	Compound A 100nM	Compound A 250nM	Compound A 500nM
Binimetinib 25 nM	1.57049	1.6855	1.51394	1.54333	0.74303	0.23806	0.07988	0.00293
Binimetinib 50 nM	1.78444	1.57824	1.10552	1.1015	0.33617	0.08494	0.00687	5.98E-04
Binimetinib 100 nM	1.40574	1.90927	0.81771	0.53885	0.15853	0.04623	0.00308	1.07E-04
Binimetinib 250 nM	2.92199	1.67399	0.69022	0.233	0.0771	0.03398	0.00408	1.07E-04
Binimetinib 500 nM	2.19283	0.50712	0.29592	0.13935	0.06226	0.02526	0.00273	5.07E-04
Binimetinib 1000 nM	1.38598	0.3404	0.14626	0.12693	0.08277	0.02281	0.00192	9.26E-05
Binimetinib 2000 nM	0.73725	0.15871	0.13631	0.12471	0.08017	0.02714	0.00442	3.54E-04

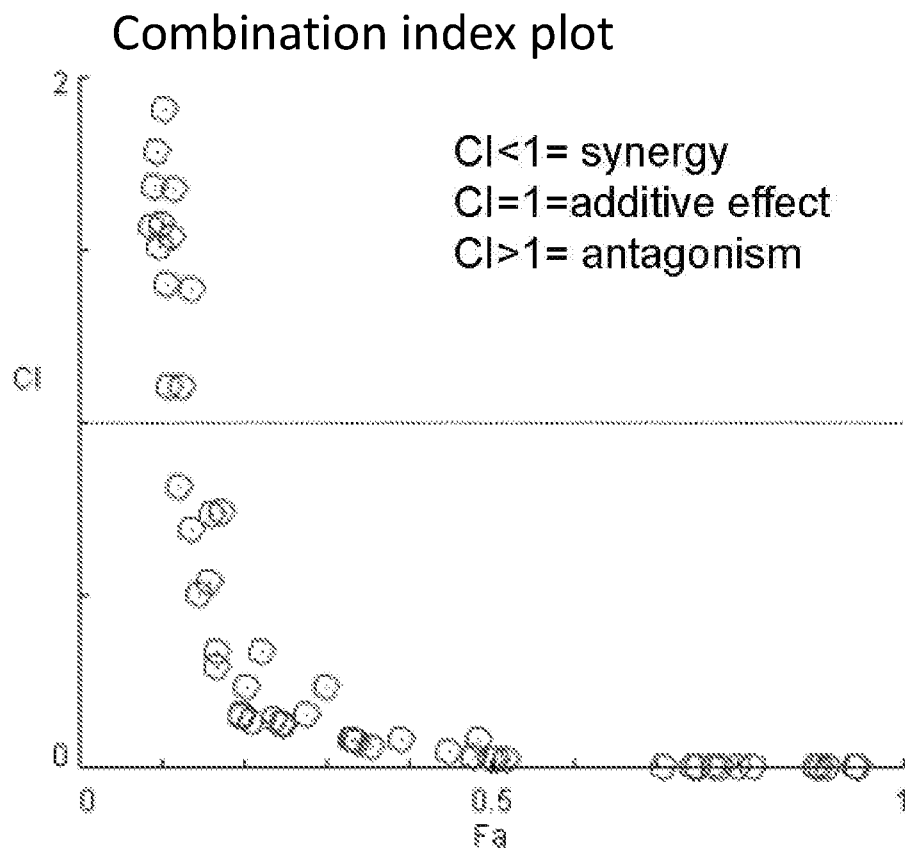
Figure 4C

Figure 5B

Cl	Compound B 1nM	Compound B 5nM	Compound B 10nM	Compound B 25nM	Compound B 50nM	Compound B 100nM	Compound B 200nM	Compound B 500nM
Binimetinib 25 nM	1.16697	1.12369	1.92347	1.87175	1.33032	0.40022	0.08512	0.00433
Binimetinib 50 nM	0.80429	1.59151	1.83453	1.76275	0.64013	0.24461	0.04974	0.00128
Binimetinib 100 nM	2.04491	2.46708	1.33485	1.04913	0.35742	0.12945	0.03332	0.00166
Binimetinib 250 nM	1.19498	1.06822	0.83211	0.43195	0.20689	0.06245	0.01894	3.14E-05
Binimetinib 500 nM	1.32017	0.62726	0.56972	0.28981	0.15592	0.0513	0.00726	5.92E-05
Binimetinib 1000 nM	2.02996	0.4532	0.37085	0.30154	0.17875	0.06054	0.01473	0.00107
Binimetinib 2000 nM	0.8794	0.43685	0.25074	0.25665	0.1561	0.04969	0.0117	0.00191

Figure 5C

Combination index plot

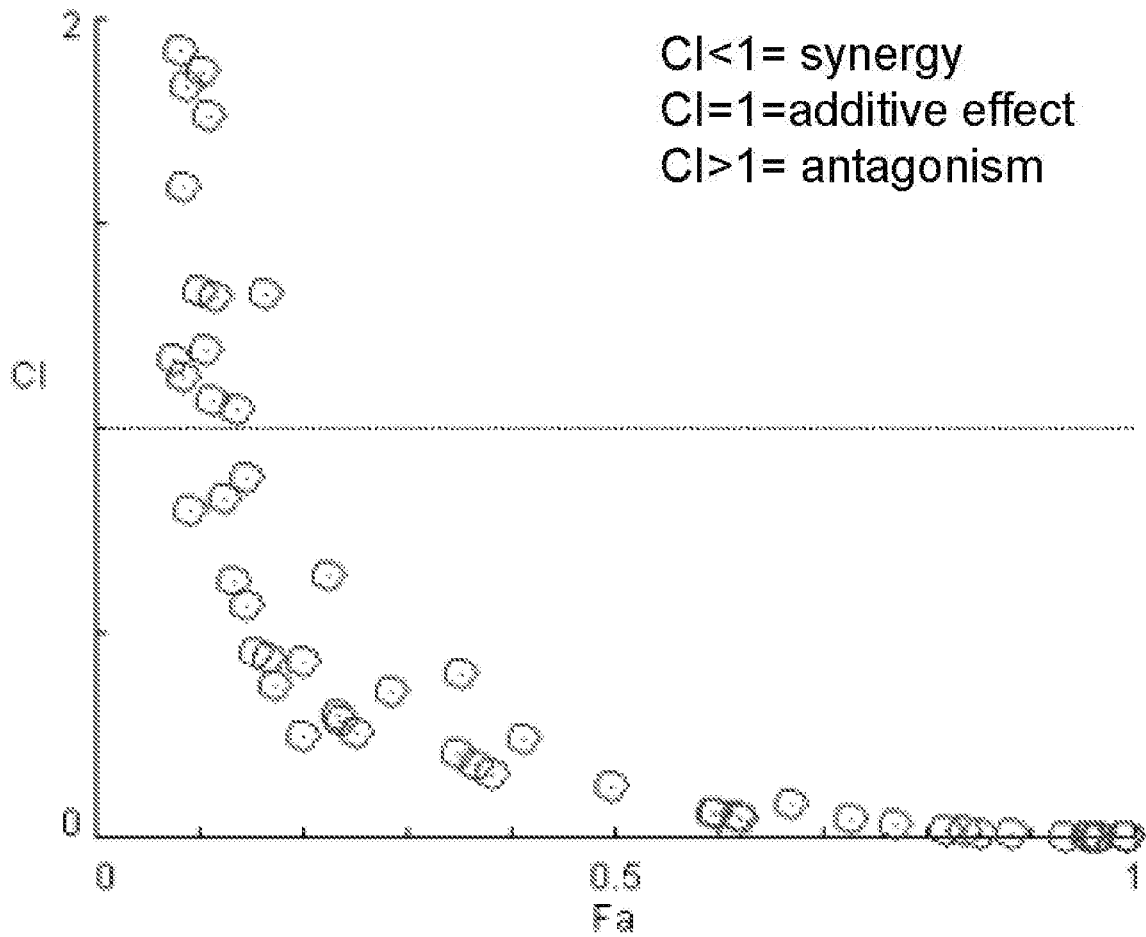


Figure 6A

Compound A and cobimetinib combination in HMC1.2 cells

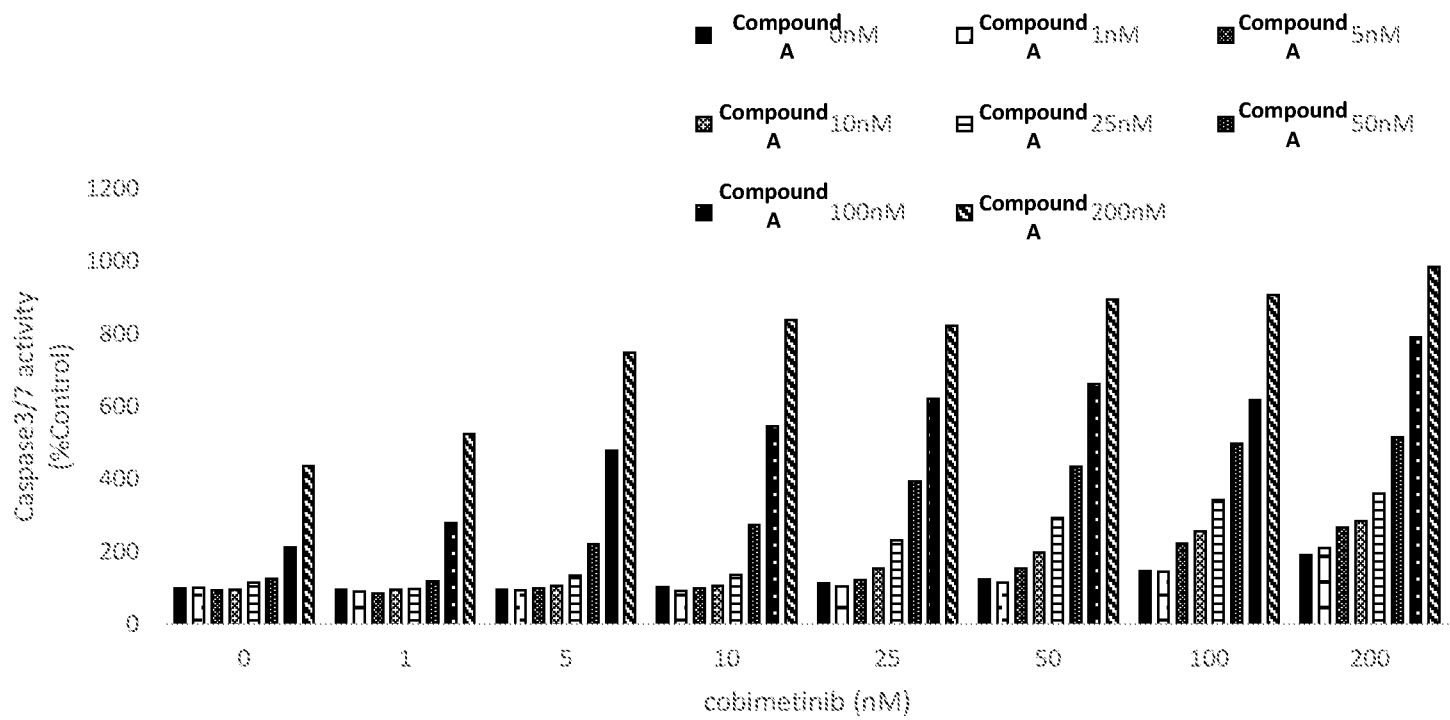
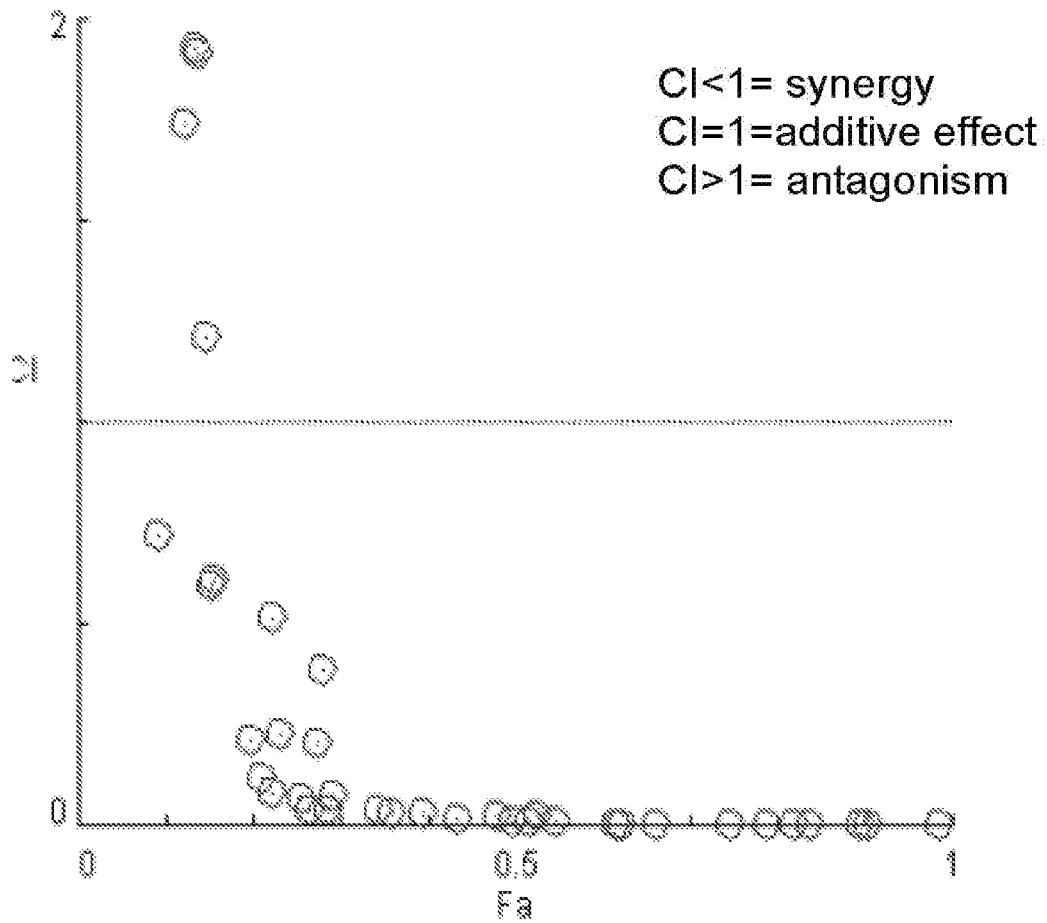


Figure 6B

Cl	Compound A 1nM	Compound A 5nM	Compound A 10nM	Compound A 25nM	Compound A 50nM	Compound A 100nM	Compound A 200nM
Cobimetinib 1 nM	0.72367	2.58457	2.84957	6.37493	5.86712	0.38735	0.02608
Cobimetinib 5 nM	2.03327	2.22709	2.49475	1.92929	0.5199	0.02364	0.00107
Cobimetinib 10 nM	4.07508	3.47138	3.05888	1.91627	0.20704	0.00993	1.78E-04
Cobimetinib 25 nM	4.08228	1.74076	0.60978	0.22536	0.03575	0.0036	2.63E-04
Cobimetinib 50 nM	3.97974	0.59607	0.21652	0.07886	0.02071	0.00202	3.67E-05
Cobimetinib 100 nM	1.21021	0.08536	0.0658	0.03731	0.00925	0.00381	2.38E-05
Cobimetinib 200 nM	0.11777	0.03679	0.04185	0.02953	0.00733	2.49E-04	4.83E-08

Figure 6C

Combination index plot



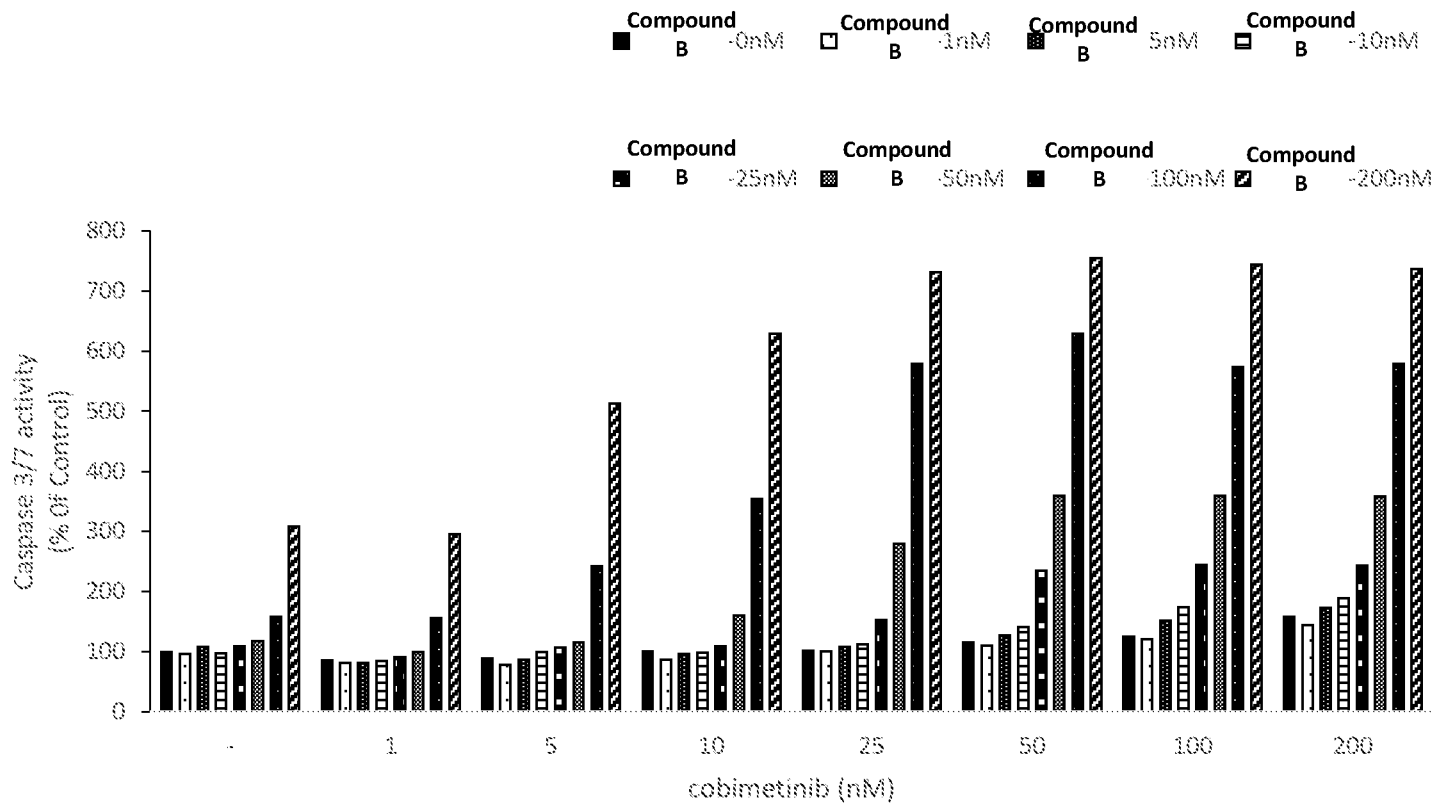


Figure 7B

Cl	Compound B 1nM	Compound B 5nM	Compound B 10nM	Compound B 25nM	Compound B 50nM	Compound B 100nM	Compound B 200nM
Cobimetinib 1 nM	1.39961	3.77808	5.66631	9.38659	11.3003	2.06695	0.08926
Cobimetinib 5 nM	5.34532	4.24727	2.63326	4.01626	5.27338	0.1571	0.00124
Cobimetinib 10 nM	4.35207	2.99291	3.57716	3.86343	0.87975	0.01274	1.33E-04
Cobimetinib 25 nM	2.75567	1.98415	2.09289	0.60486	0.03221	1.80E-04	1.49E-05
Cobimetinib 50 nM	2.28329	0.93831	0.593	0.04964	0.00576	6.67E-05	8.50E-06
Cobimetinib 100 nM	1.88398	0.34755	0.17375	0.03918	0.00578	1.98E-04	1.09E-05
Cobimetinib 200 nM	0.79643	0.18837	0.12431	0.04216	0.00592	1.77E-04	1.29E-05

Figure 7C

Combination index plot

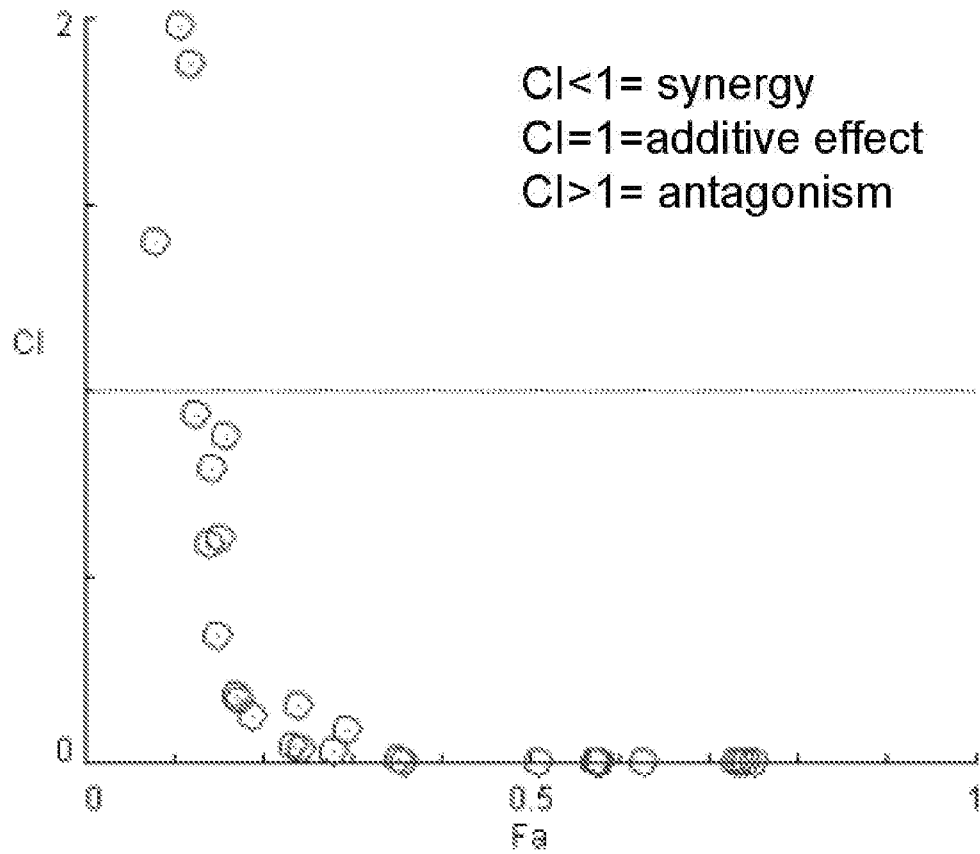


Figure 8B

Cl	Compound A 1nM	Compound A 5nM	Compound A 10nM	Compound A 25nM	Compound A 50nM	Compound A 100nM	Compound A 250nM	Compound A 500nM
Ulixertinib 50 nM	1.60258	2.92097	2.92056	2.33011	3.16429	3.40419	0.95172	0.0969
Ulixertinib 100 nM	2.34725	1.48965	1.55963	2.64283	2.89453	2.47874	0.83763	0.0861
Ulixertinib 250 nM	2.52682	1.04818	1.63023	1.59316	3.17247	2.16888	0.71586	0.03154
Ulixertinib 500 nM	0.5764	0.68476	1.29507	1.07784	1.14575	0.51154	0.12022	0.00349
Ulixertinib 1000 nM	0.25087	0.36296	0.45054	0.83564	0.31409	0.5004	0.065	2.04E-04
Ulixertinib 2000 nM	0.34059	0.33951	0.63595	0.77262	0.96933	0.75802	0.15375	7.35E-04
Ulixertinib 5000 nM	2.6495	5.10326	2.44488	2.61636	3.22495	2.41533	1.00502	0.03806

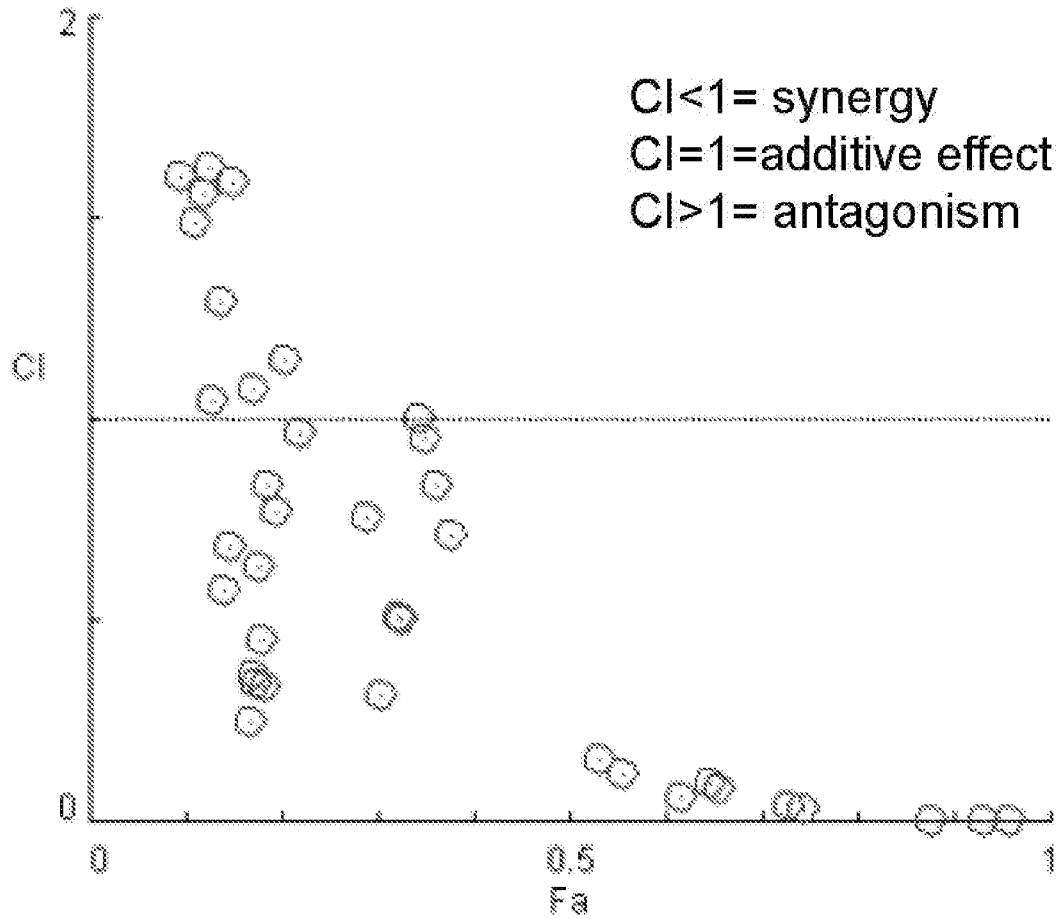
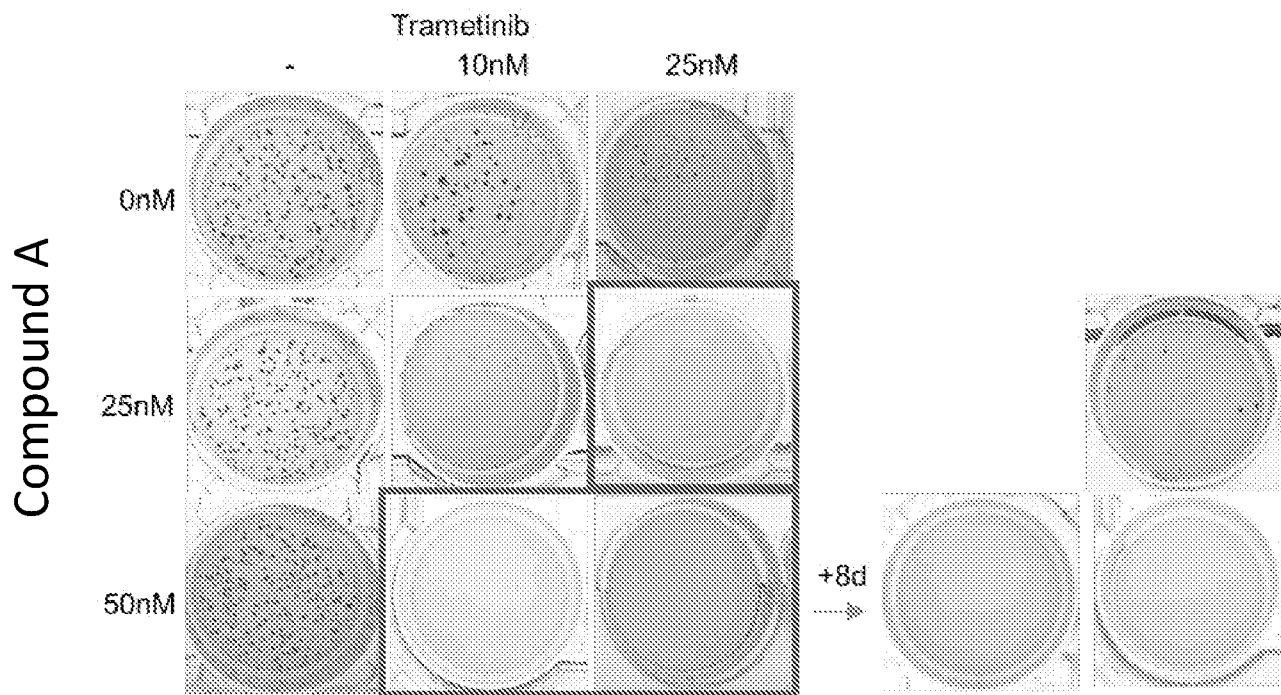
Figure 8C**Combination index plot**

Figure 9A

HMC1.2 cells

**Figure 9B**

Compound A and trametinib in HMC1.2 cells

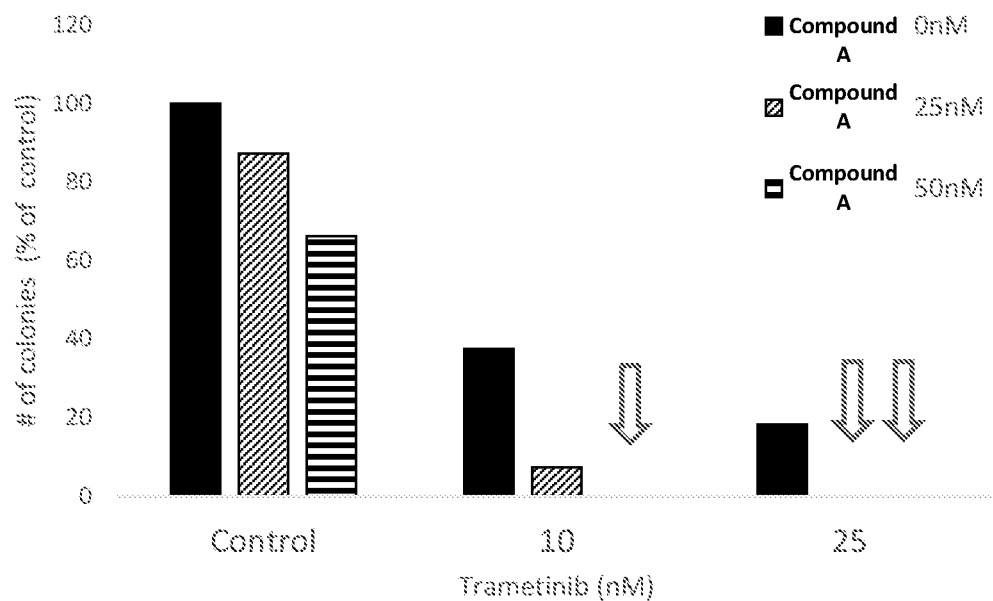


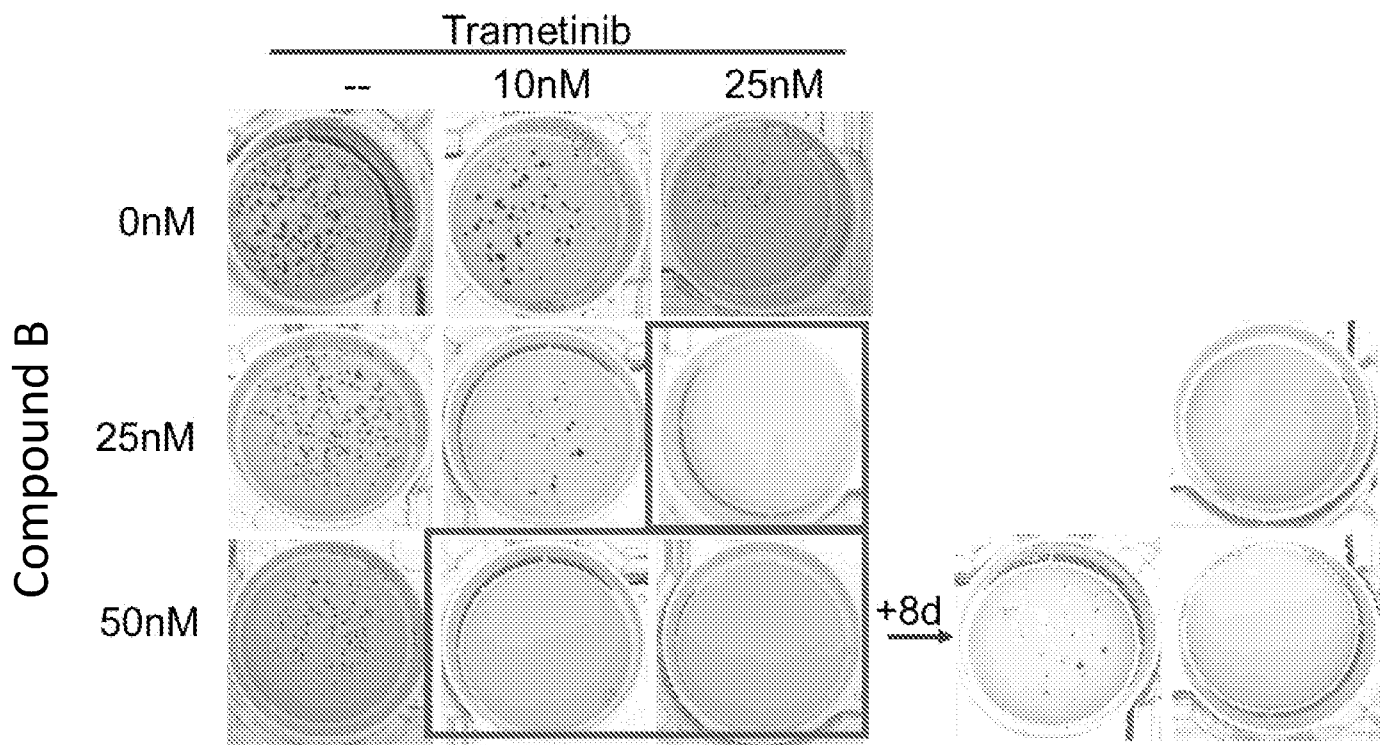
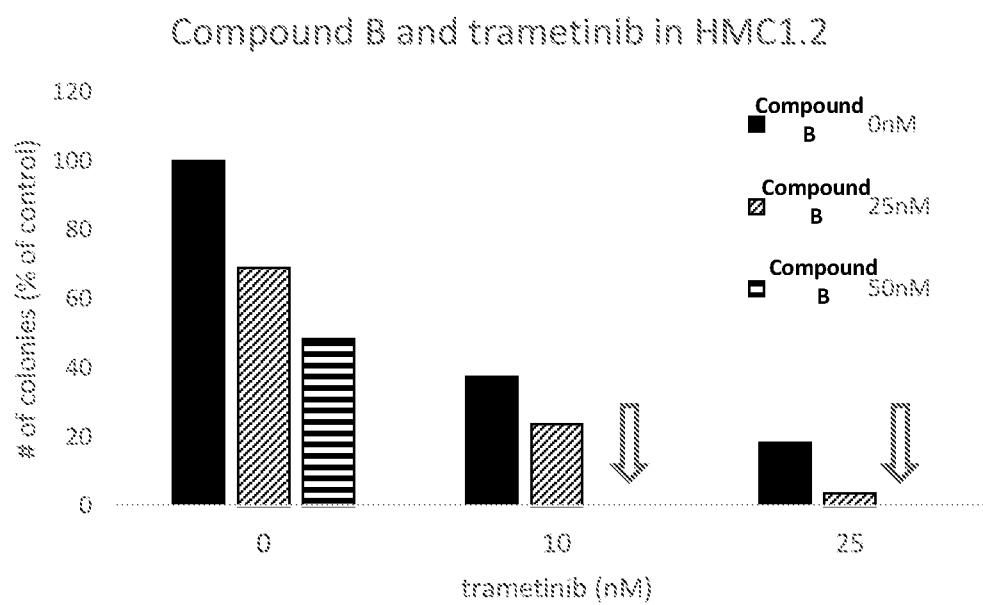
Figure 10A**Figure 10B**

Figure 11A

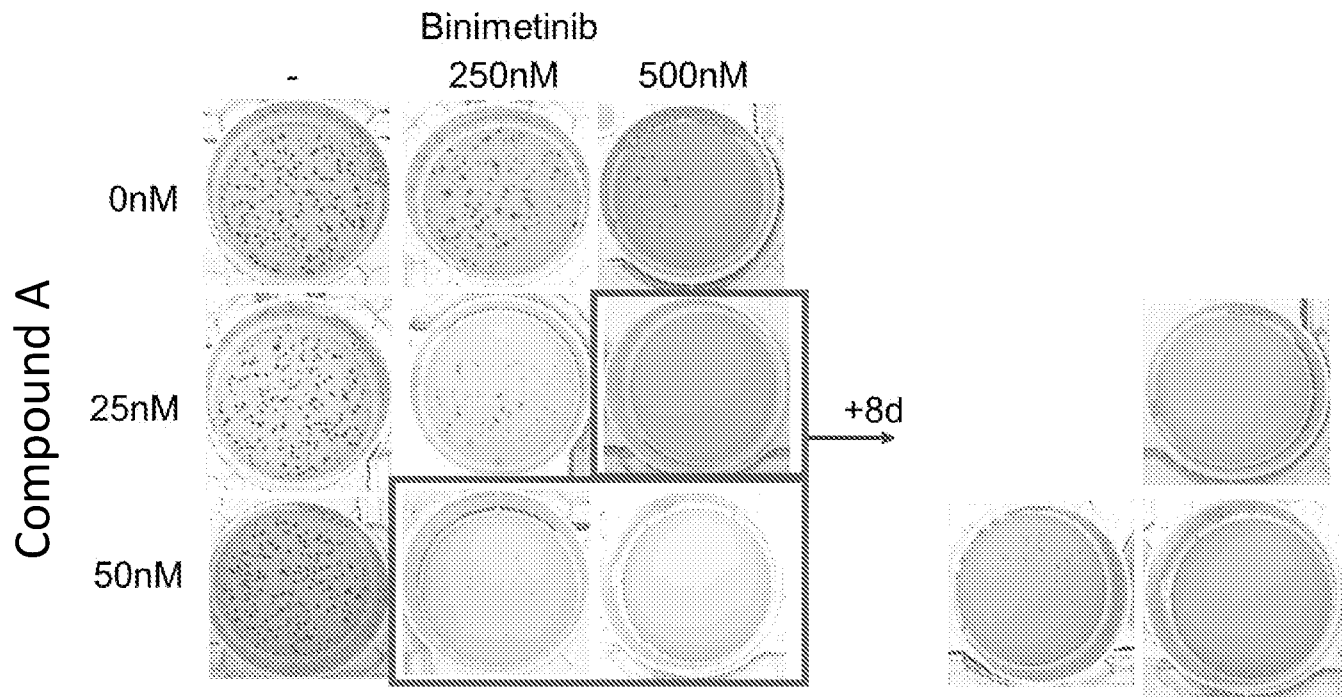


Figure 11B

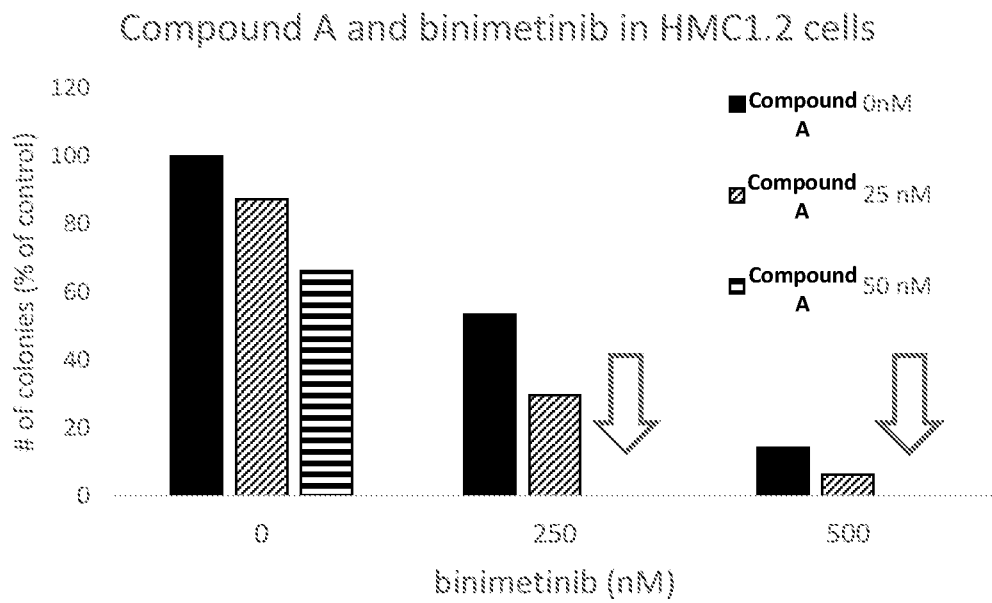


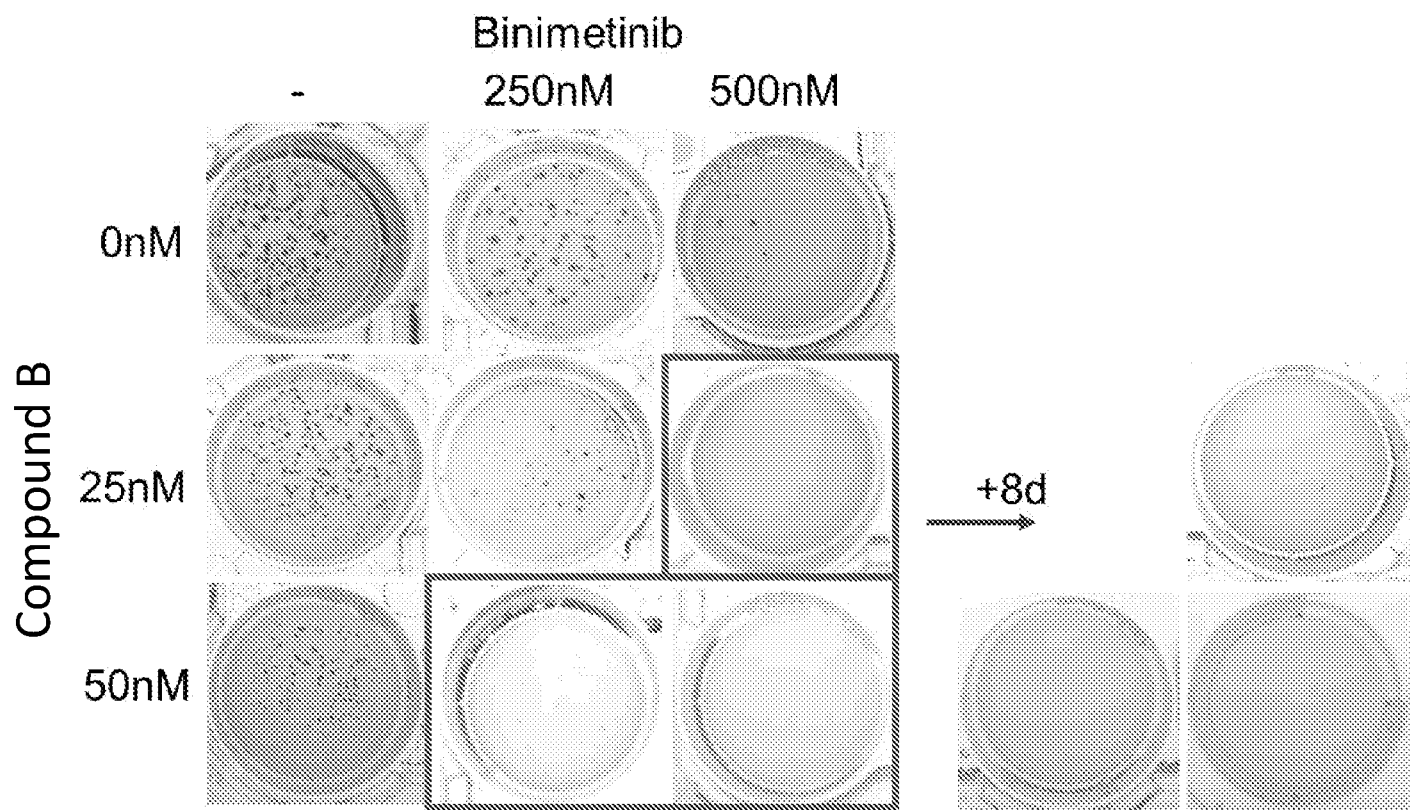
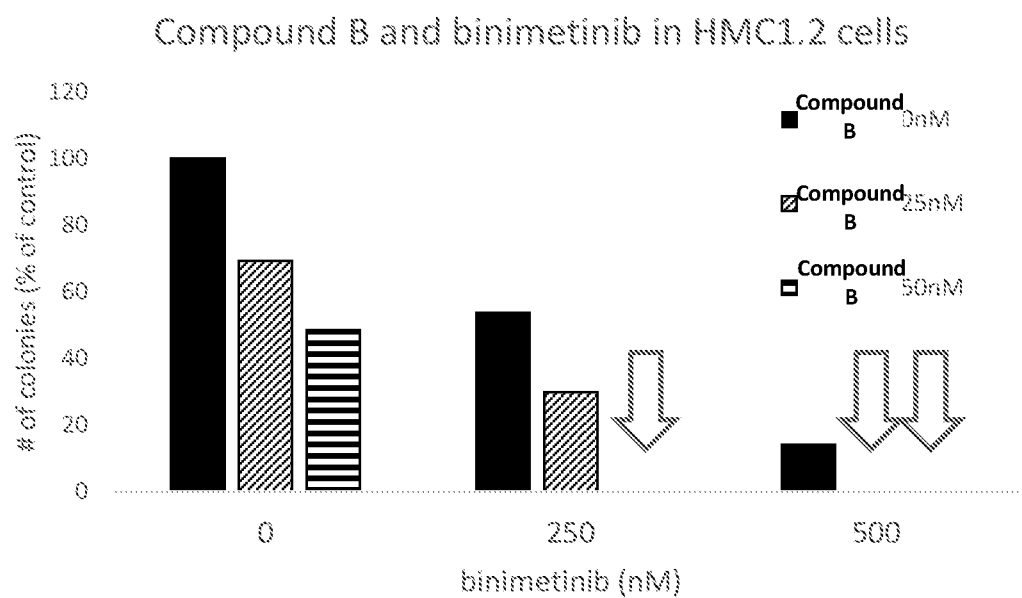
Figure 12A**Figure 12B**

Figure 13A

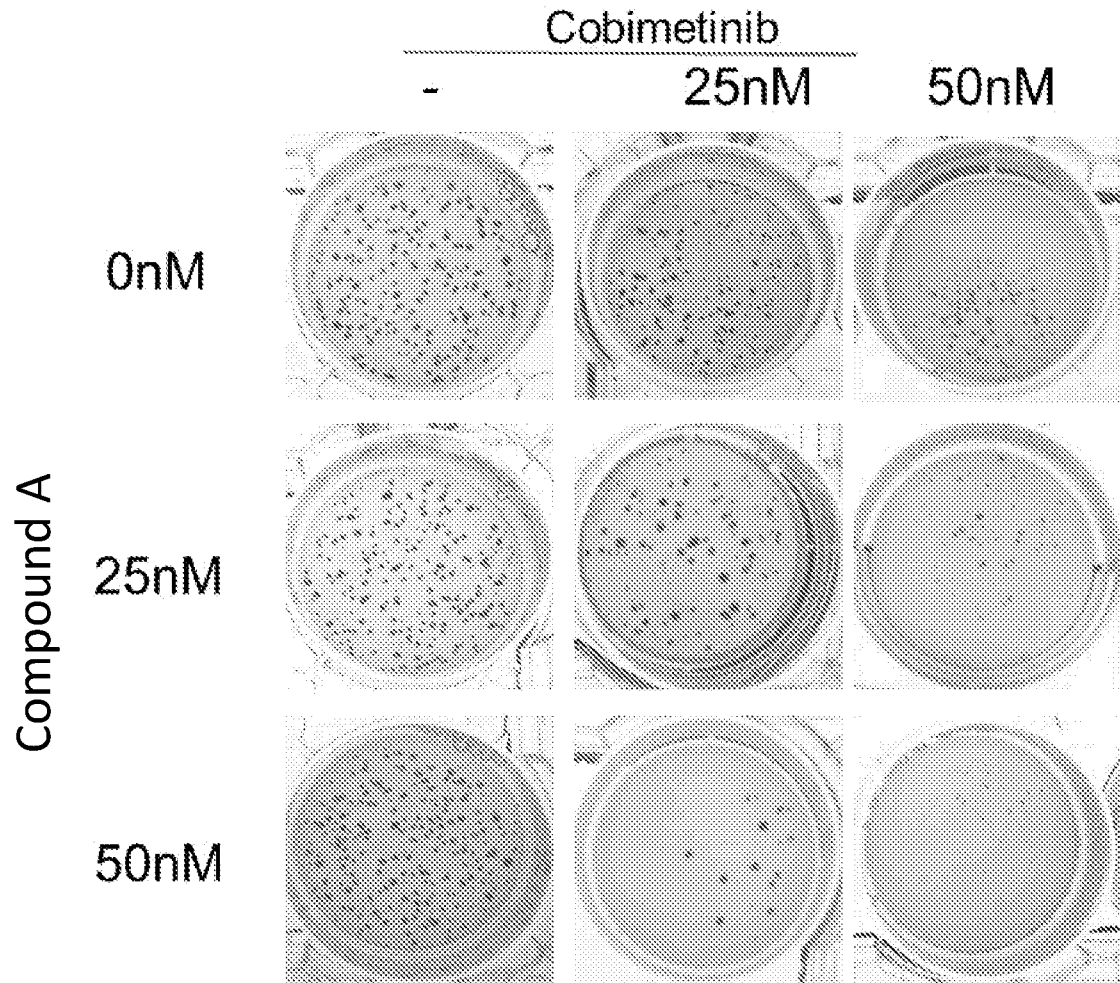


Figure 13B

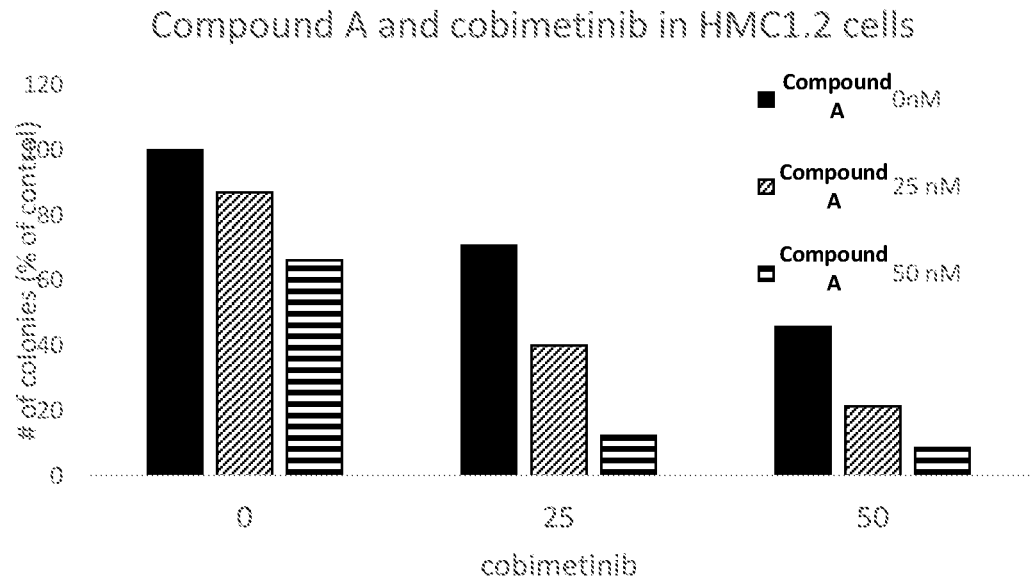


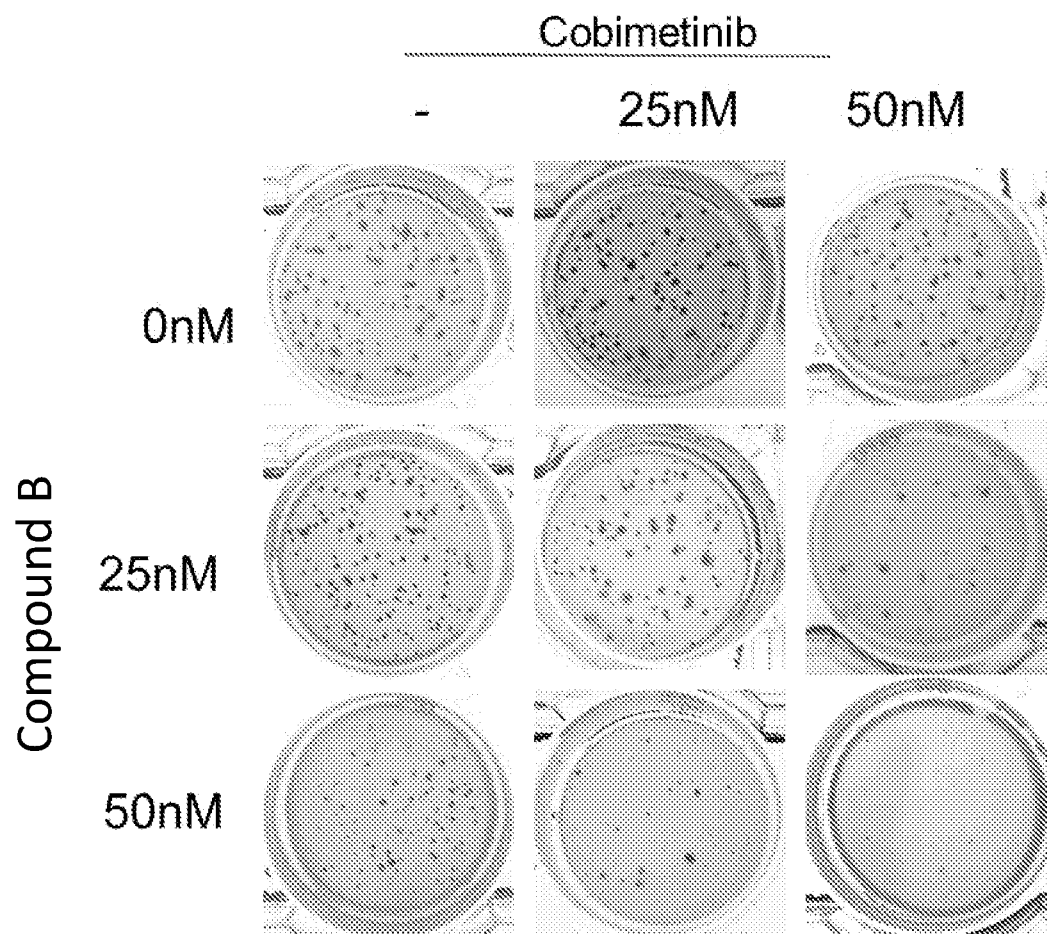
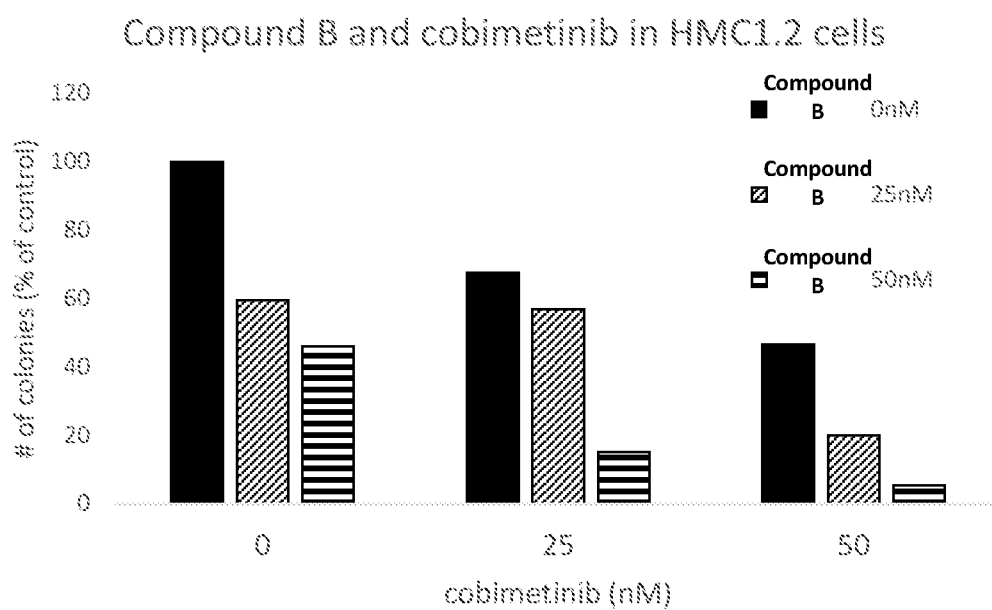
Figure 14A**Figure 14B**

Figure 15A

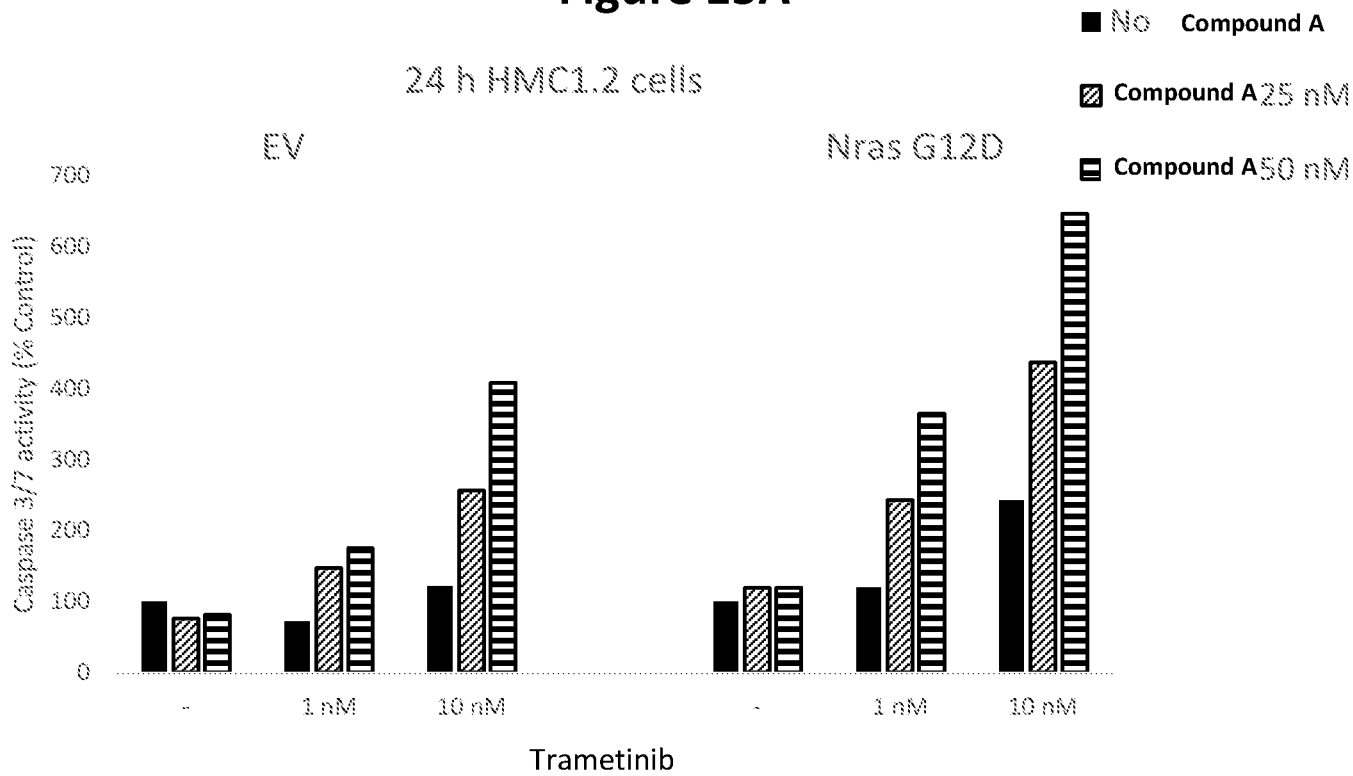


Figure 15B

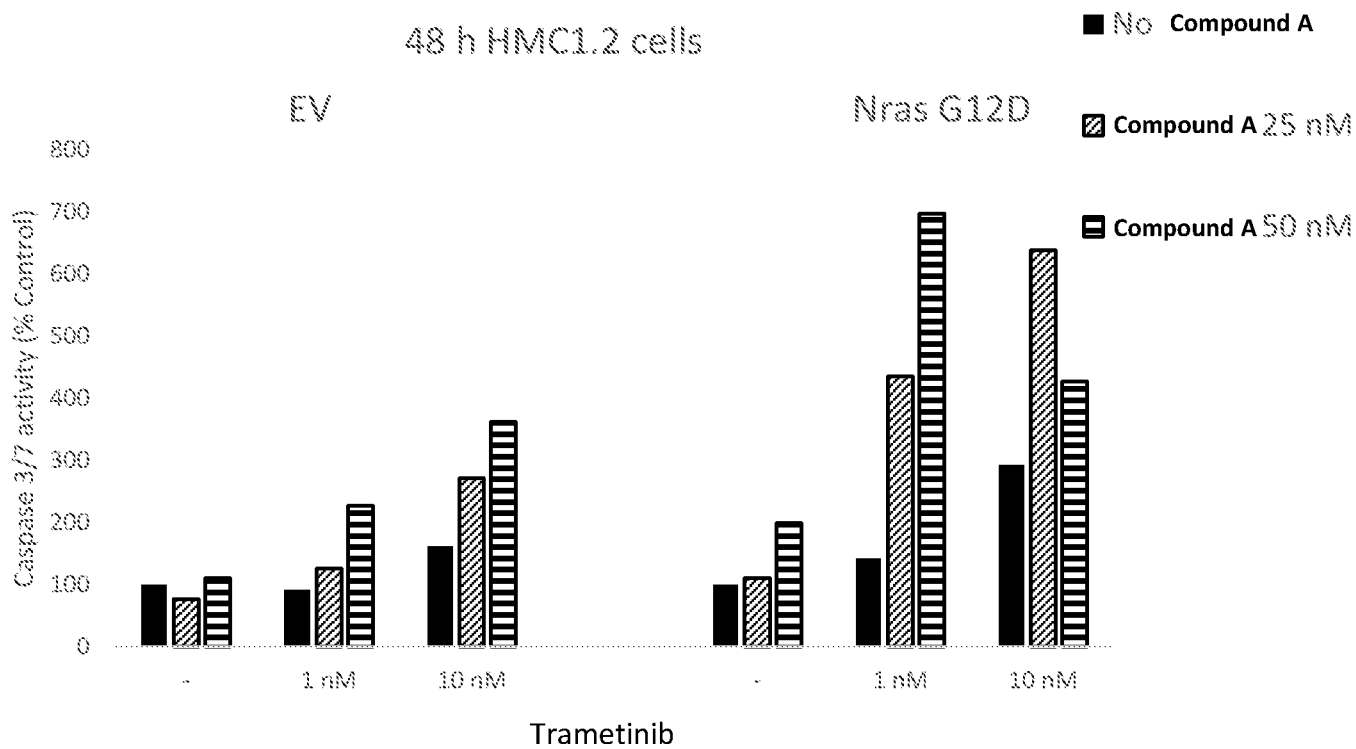


Figure 16A

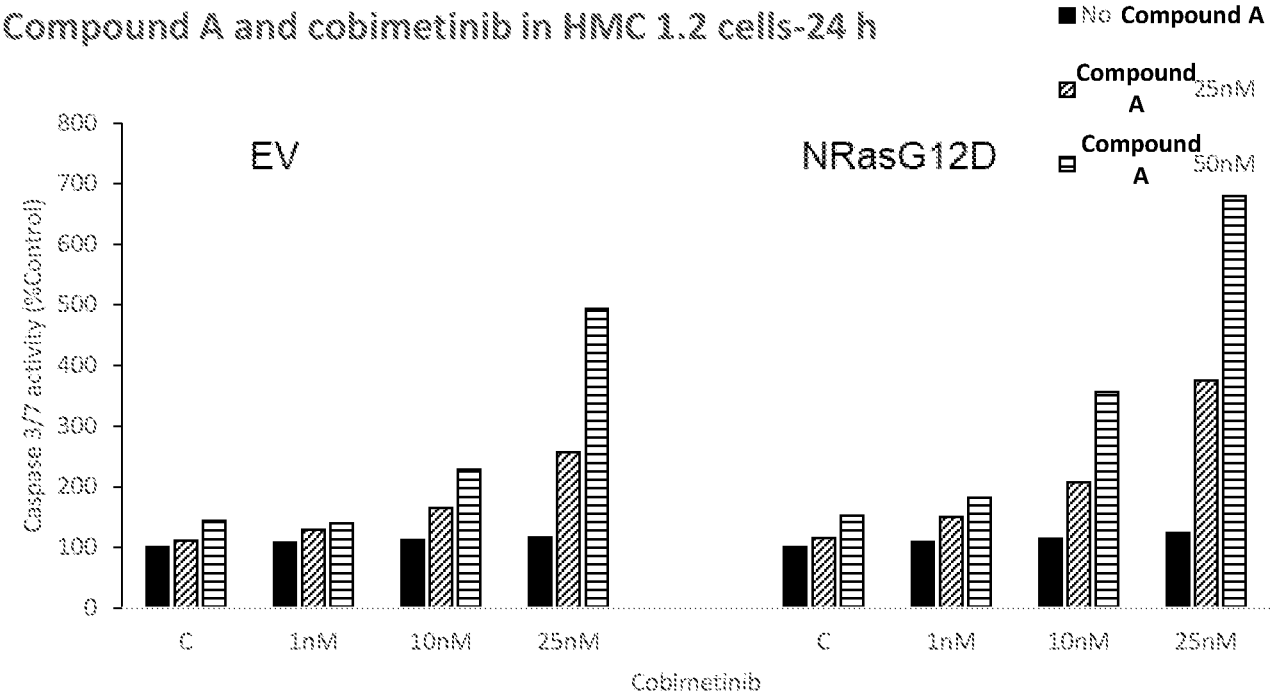


Figure 16B

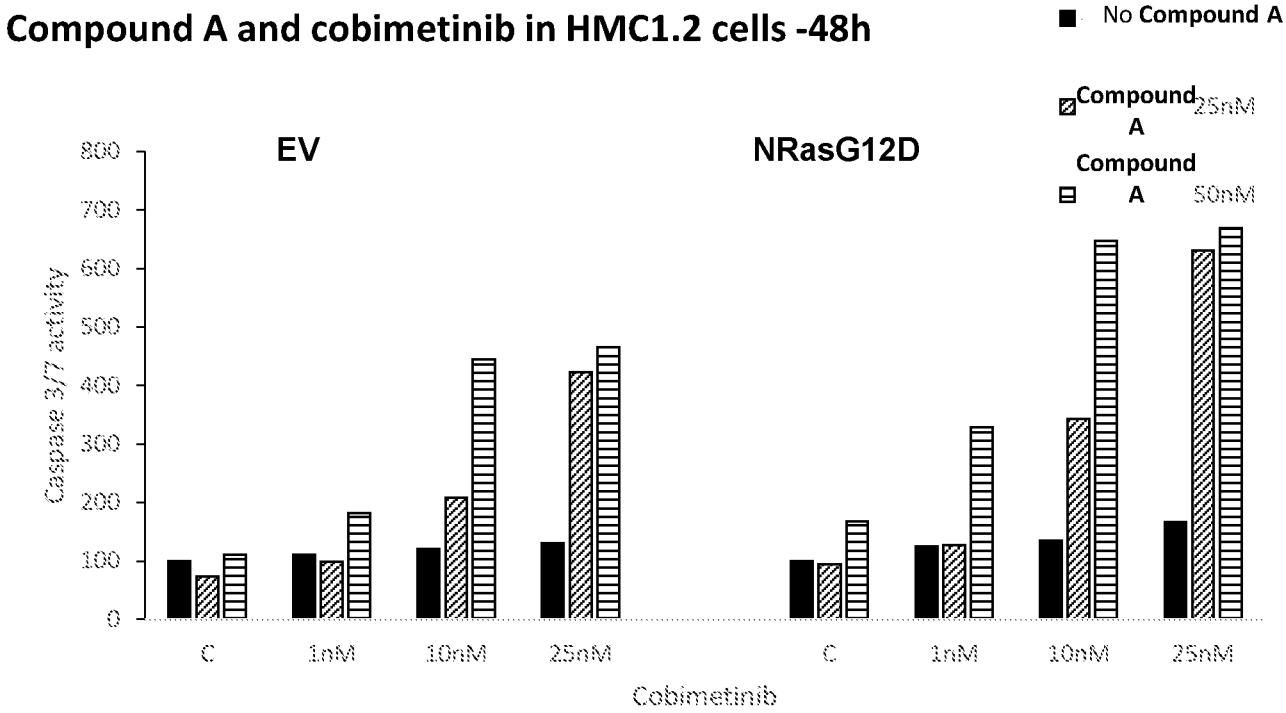


Figure 17A

HMC1.2-EV cells

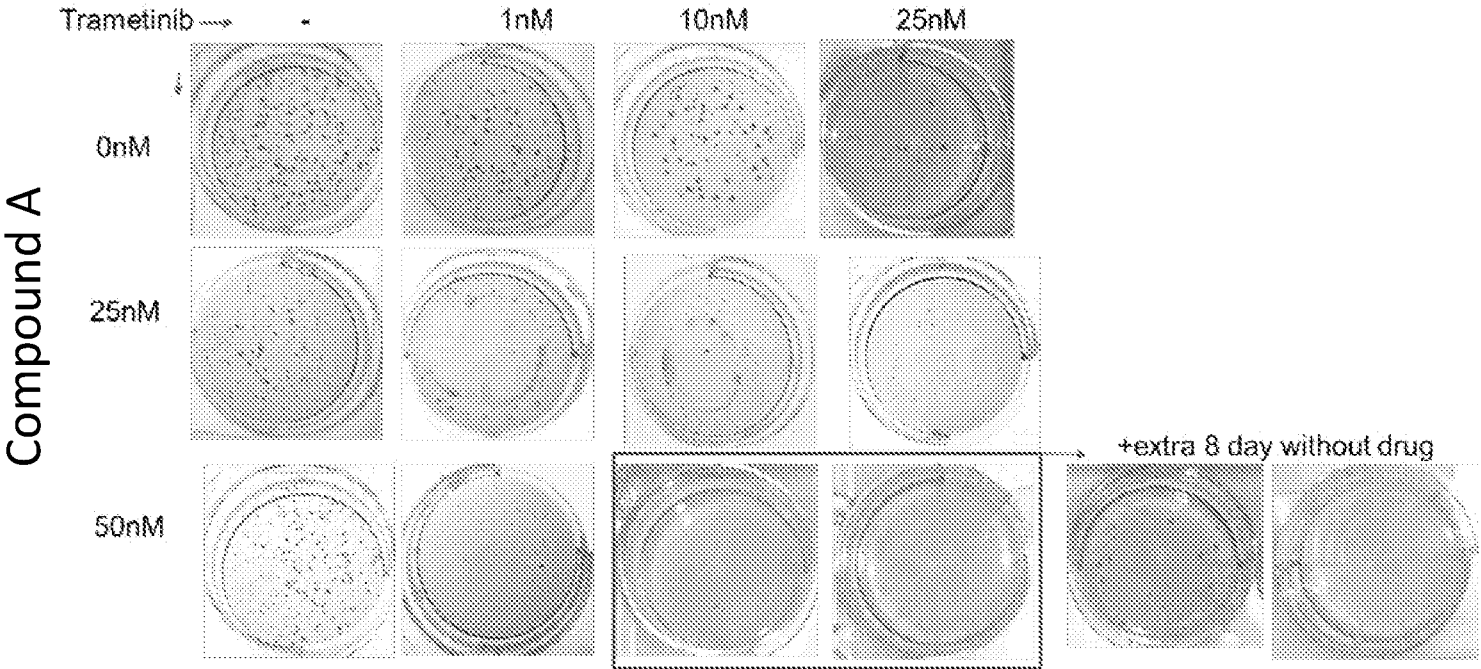


Figure 17B

HMC1.2 EV

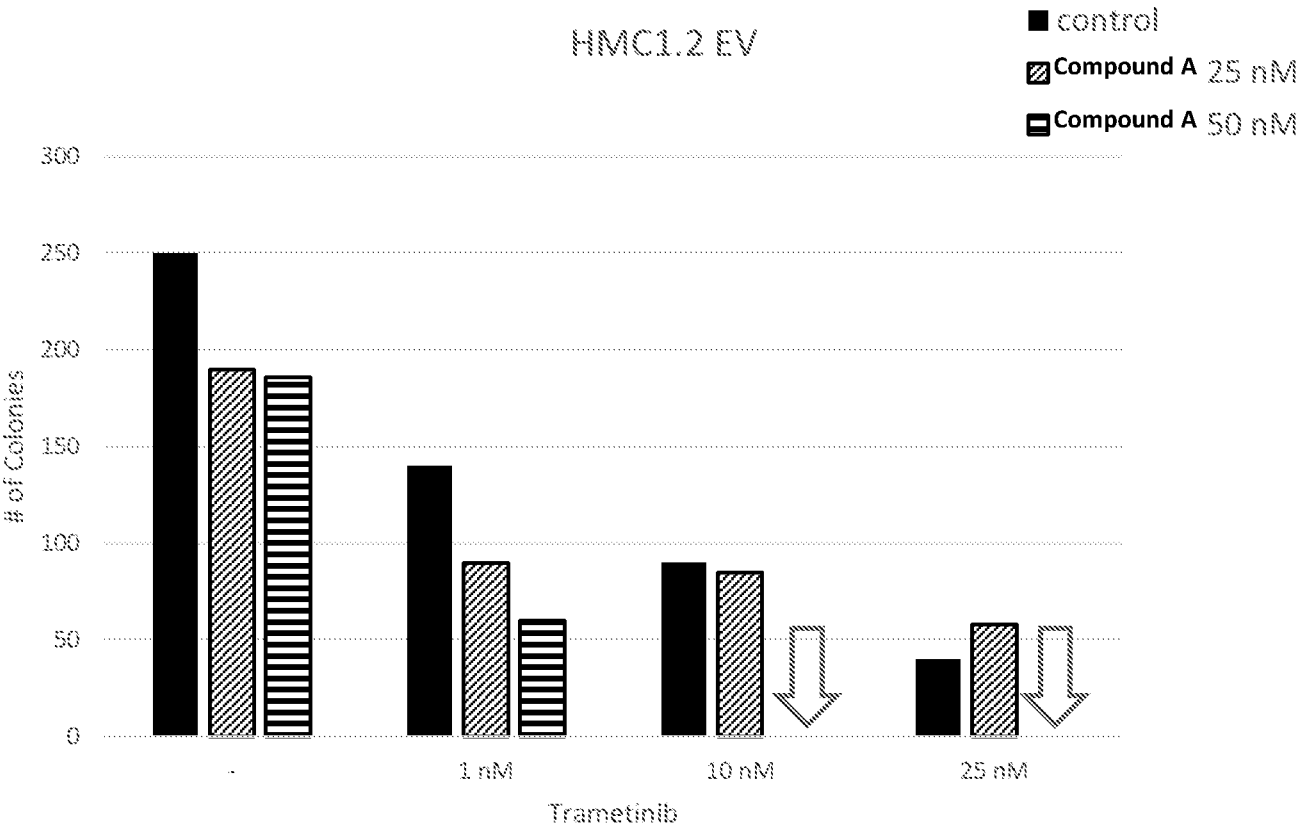
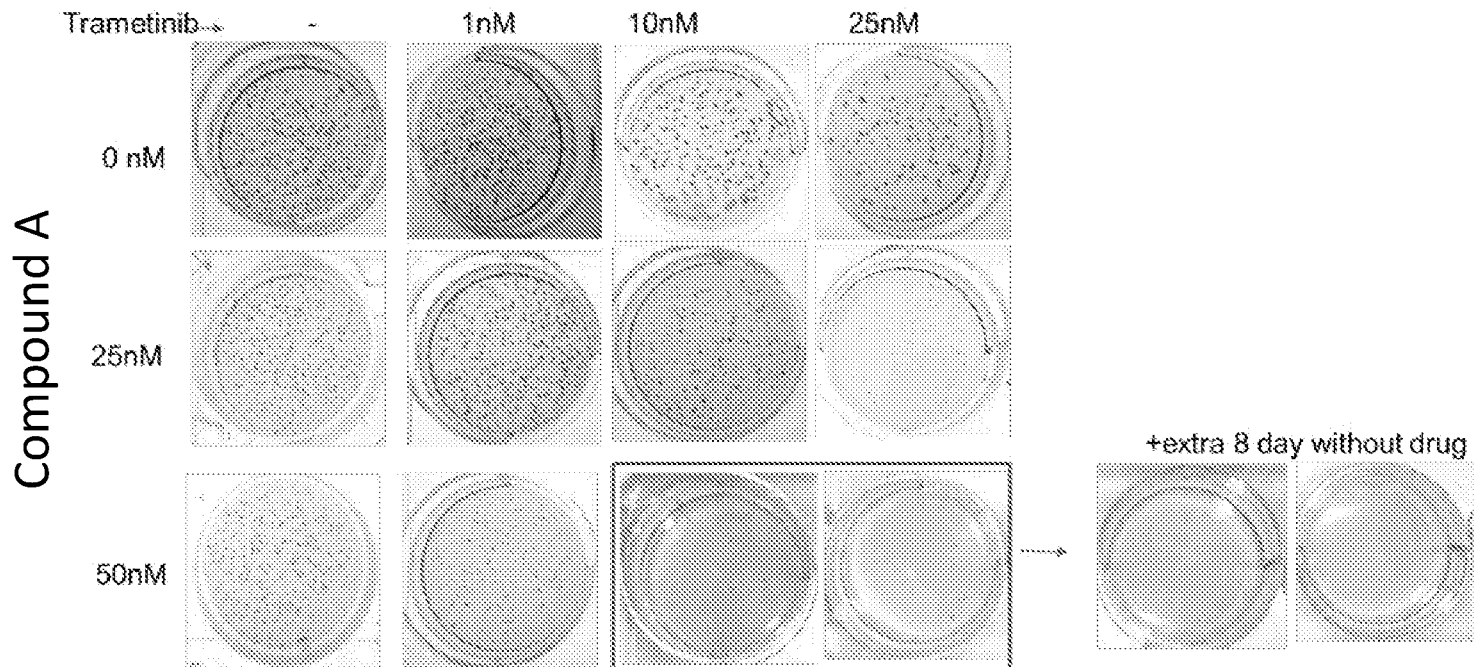


Figure 17C

HMC1.2-Nras-G12D

**Figure 17D**

HMC1.2 Nras G12D

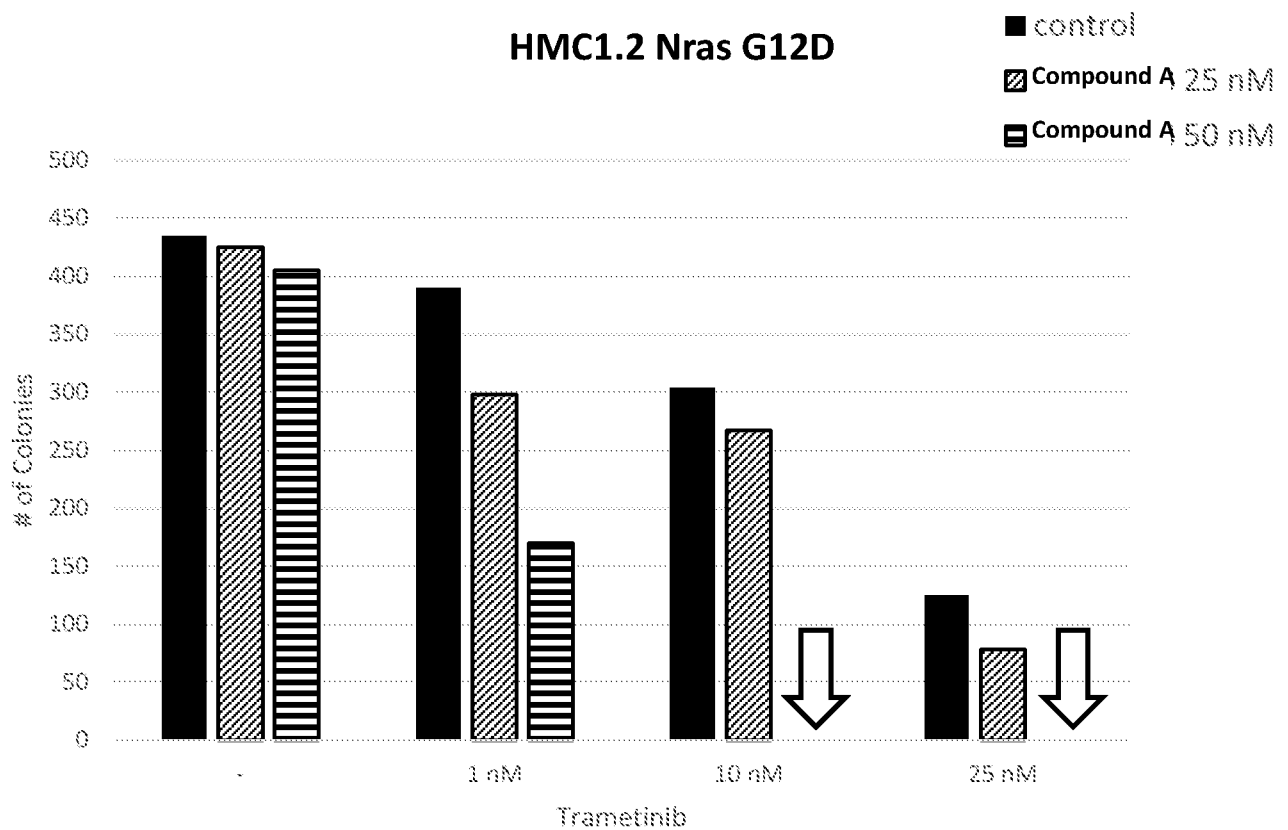


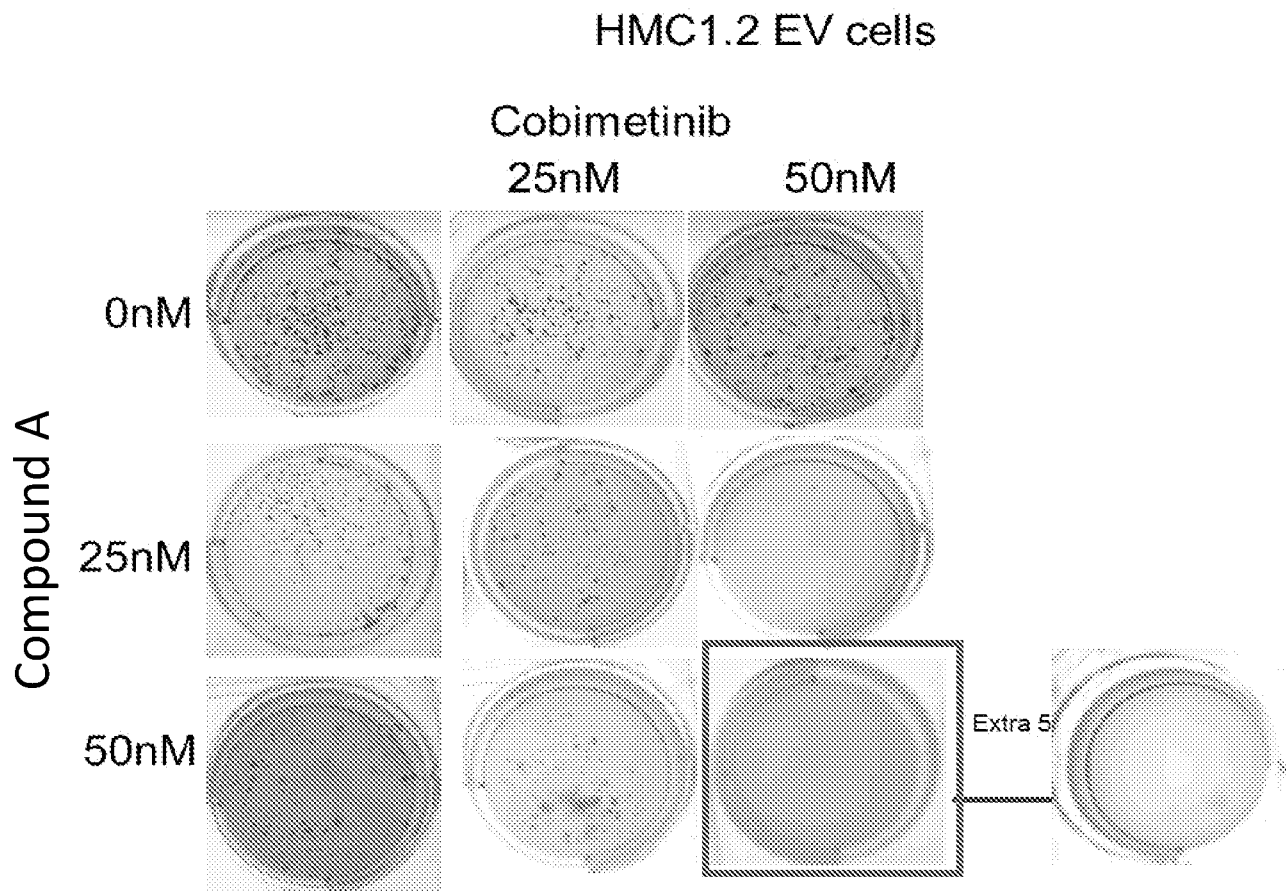
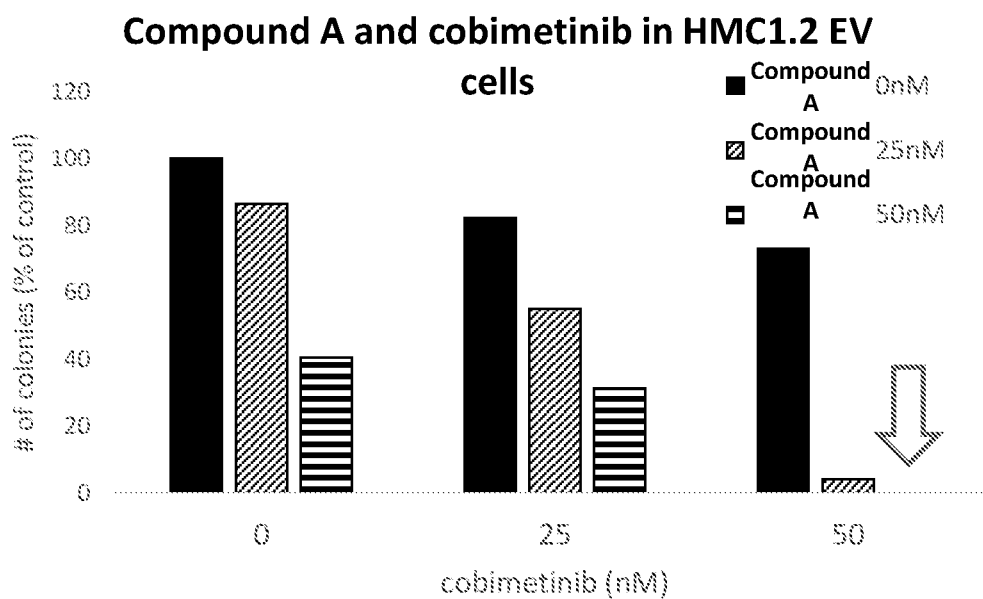
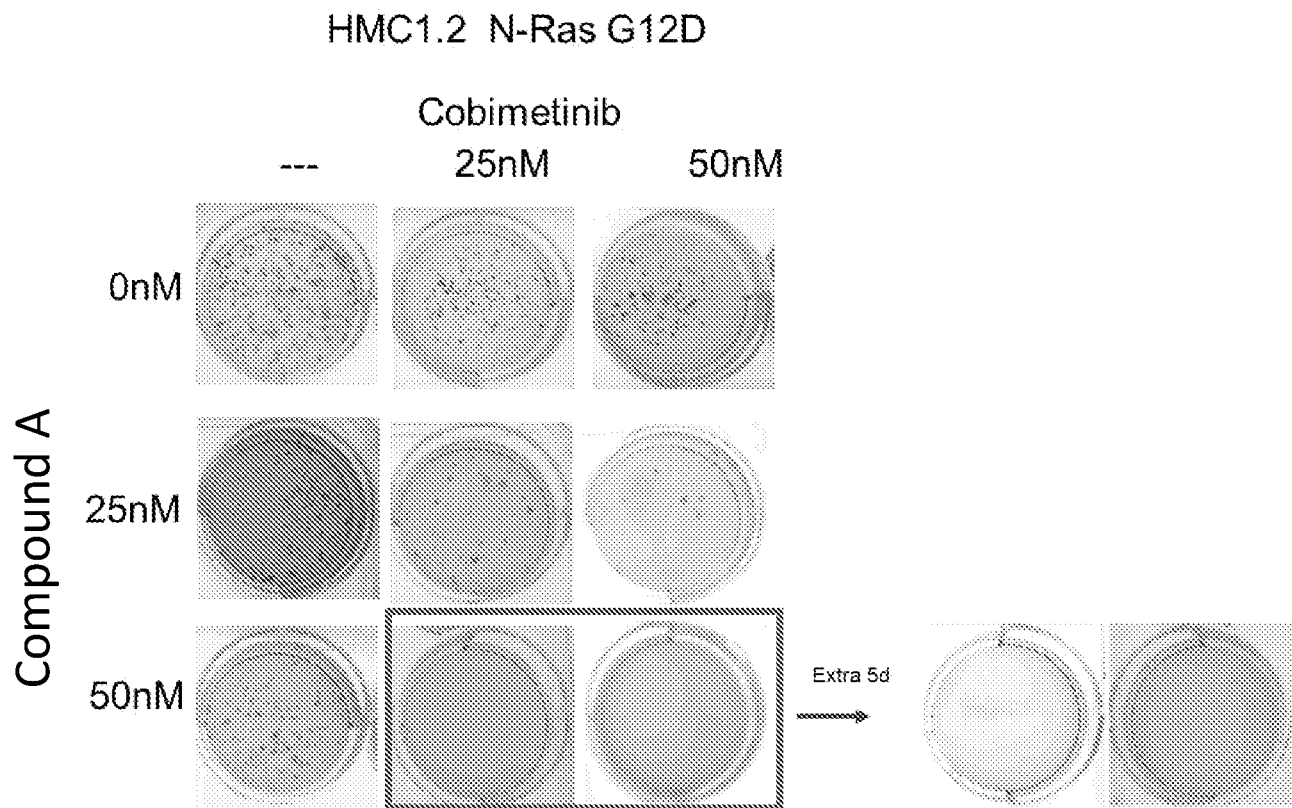
Figure 18A**Figure 18B**

Figure 18C**Figure 18D**