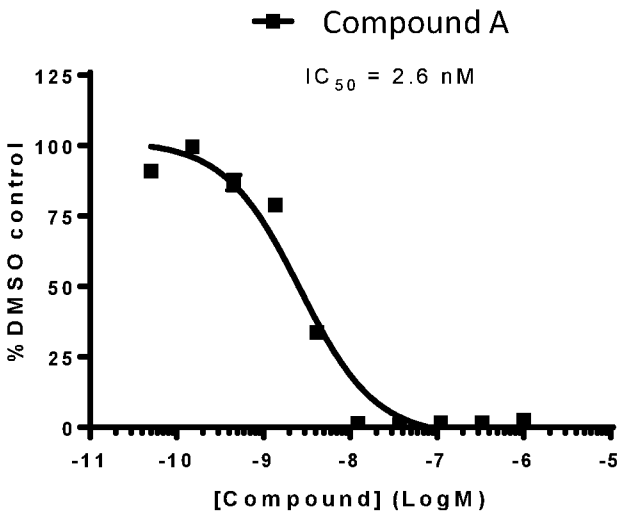
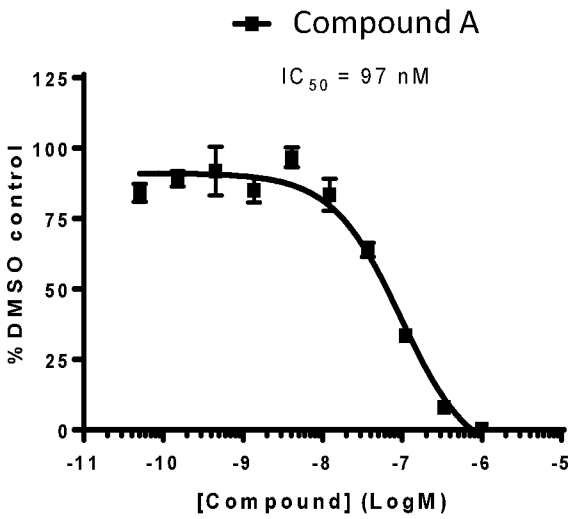
Figure 1A

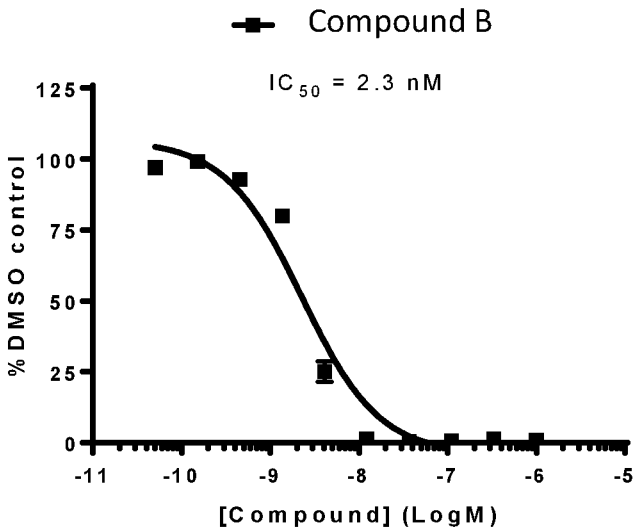


HMC1.1 V560G

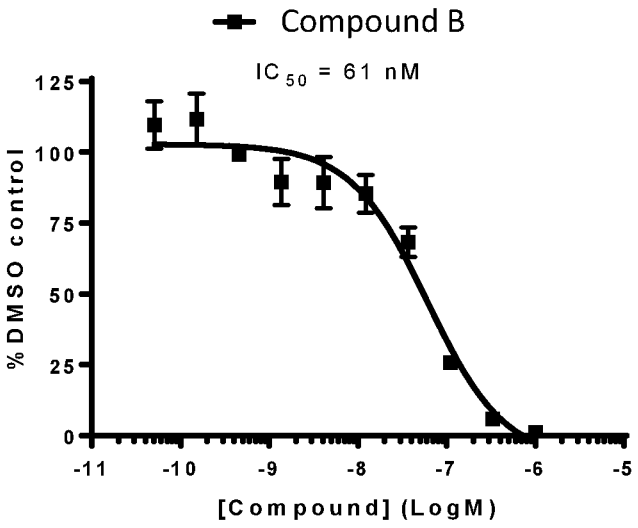


HMC1.1 V560G/D816V

Figure 1B



HMC1.1 V560G



HMC1.1 V560G/D816V

Figure 2A

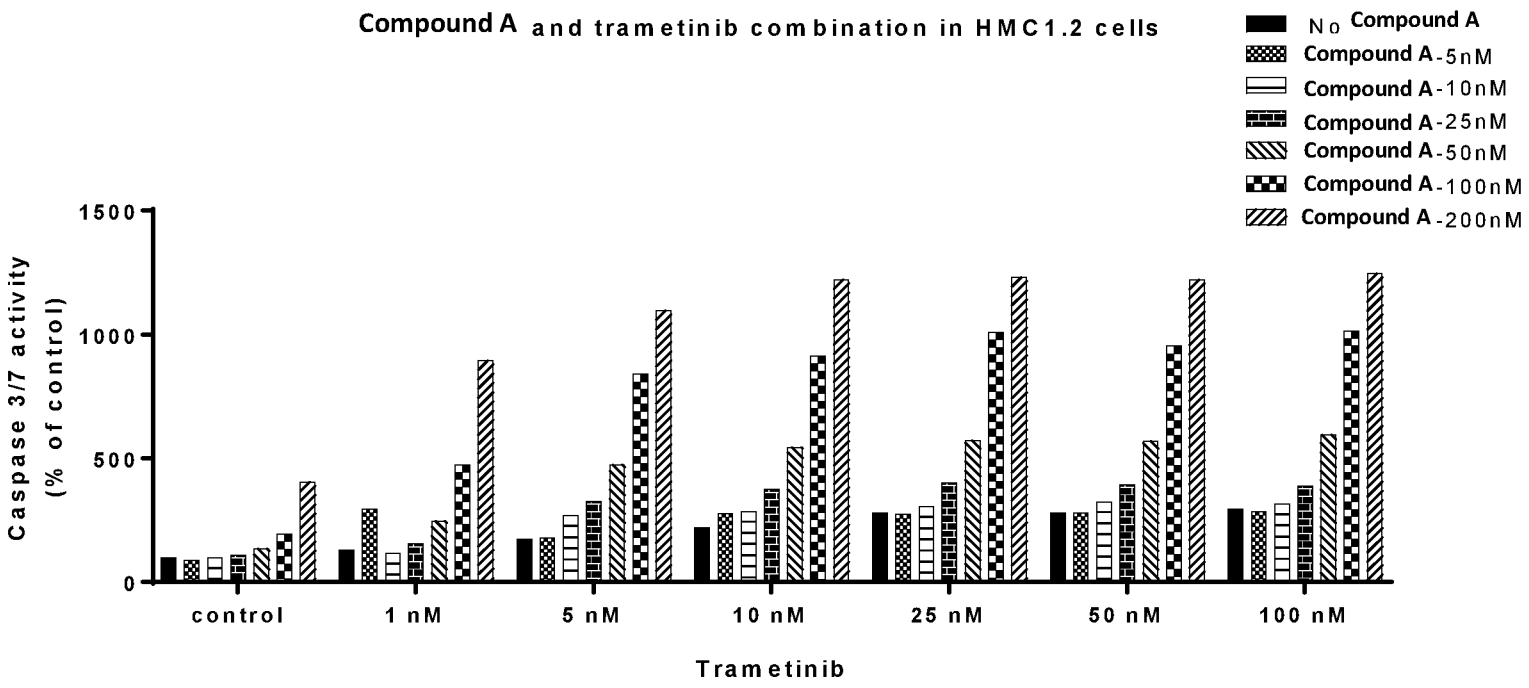

Compound A and trametinib combination in HMC1.2 cells
No Compound A
Compound A-5nM
Compound A-10nM
Compound A-25nM
Compound A-50nM
Compound A-100nM
Compound A-200nM
Caspase 3/7 activity
(% of control)
1500
1000
500
0
control
1 nM
5 nM
10 nM
25 nM
50 nM
100 nM
Trametinib

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

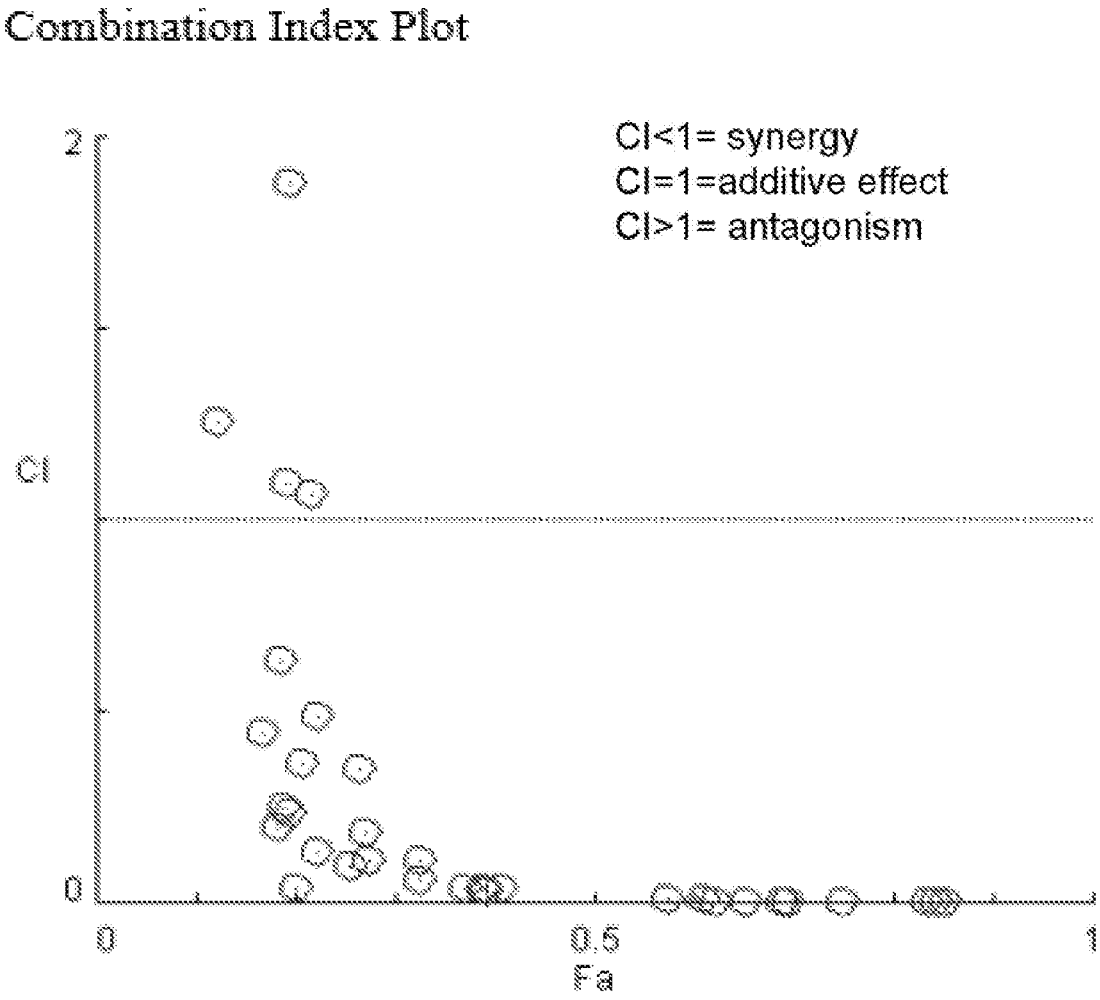

Combination Index Plot
CI<1= synergy
CI=1=additive effect
CI>1= antagonism
2
CI
0
0
0.5
1
Fa

Figure 3A

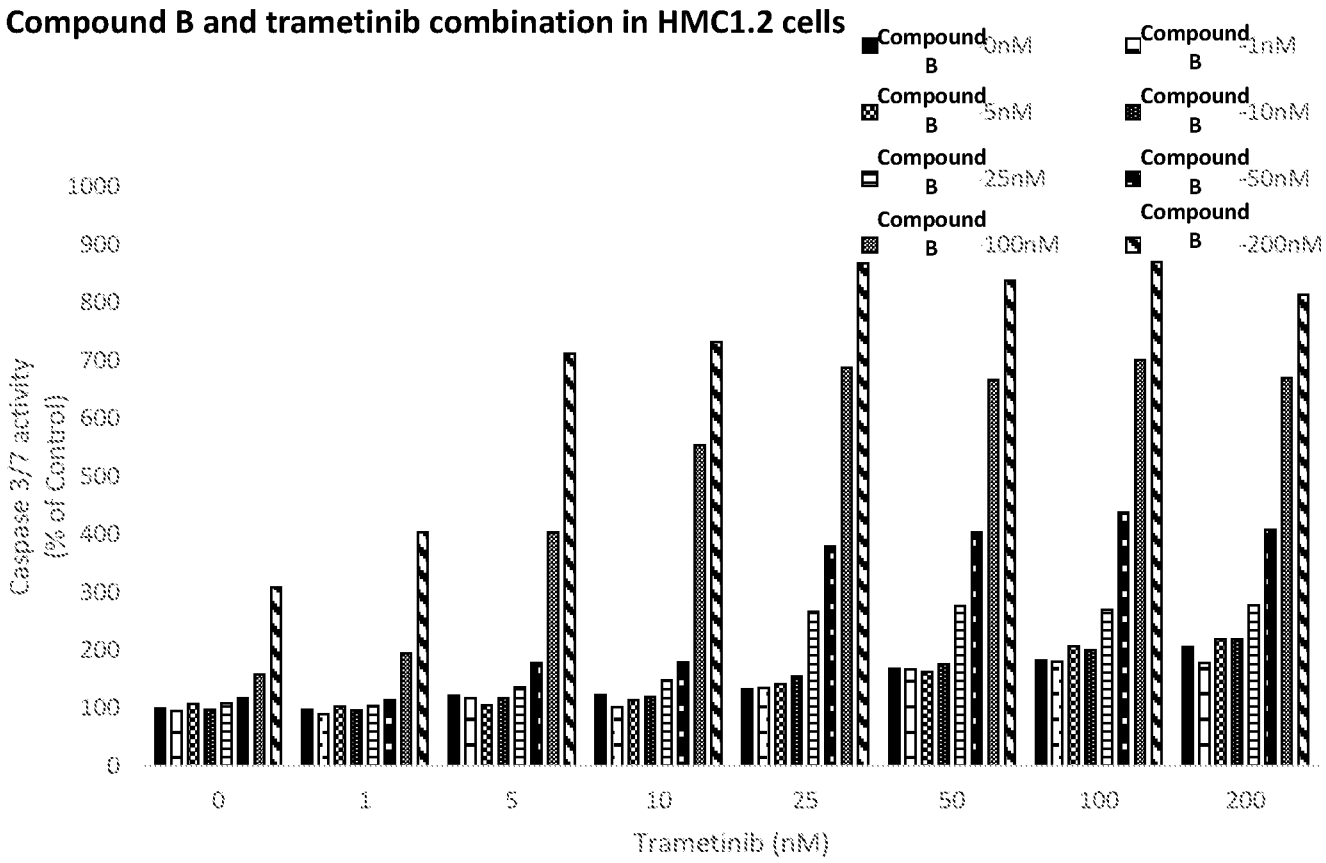

Compound B and trametinib combination in HMC1.2 cells
Compound B 0nM
Compound B 1nM
Compound B 5nM
Compound B 10nM
Compound B 25nM
Compound B 50nM
Compound B 100nM
Compound B 200nM
Caspase 3/7 activity (% of Control)
1000
900
800
700
600
500
400
300
200
100
0
0
1
5
10
25
50
100
200
Trametinib (nM)

Figure 3B

CI	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

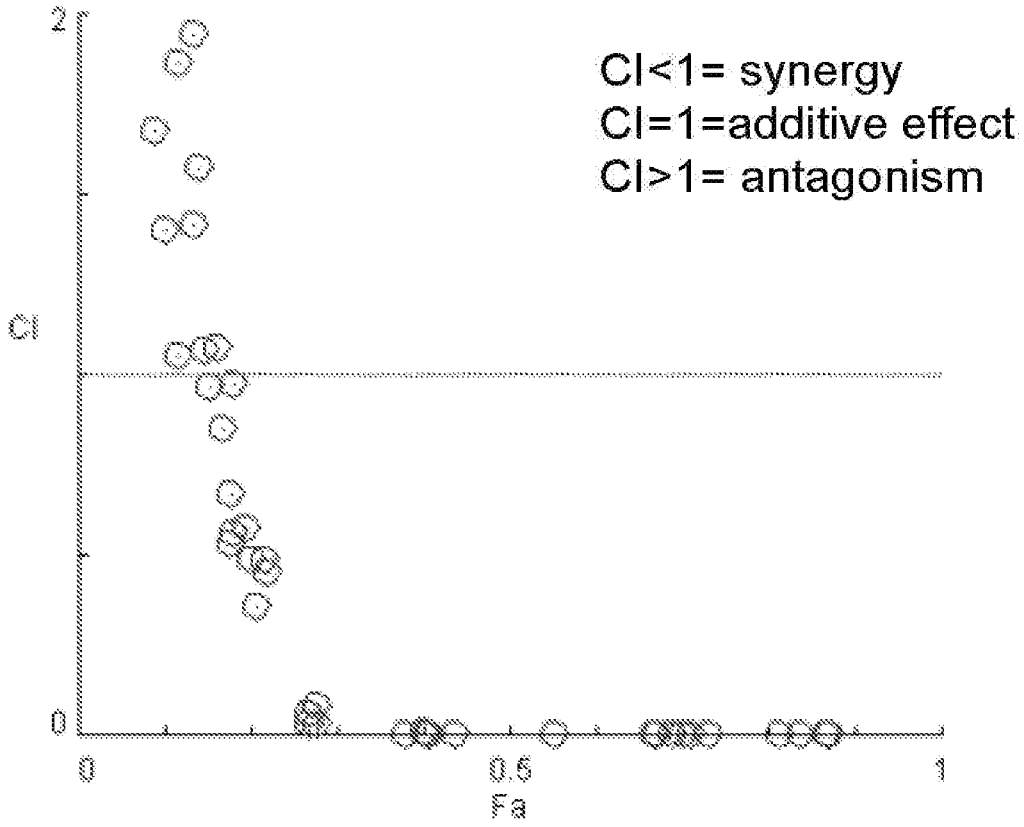


Figure 4A

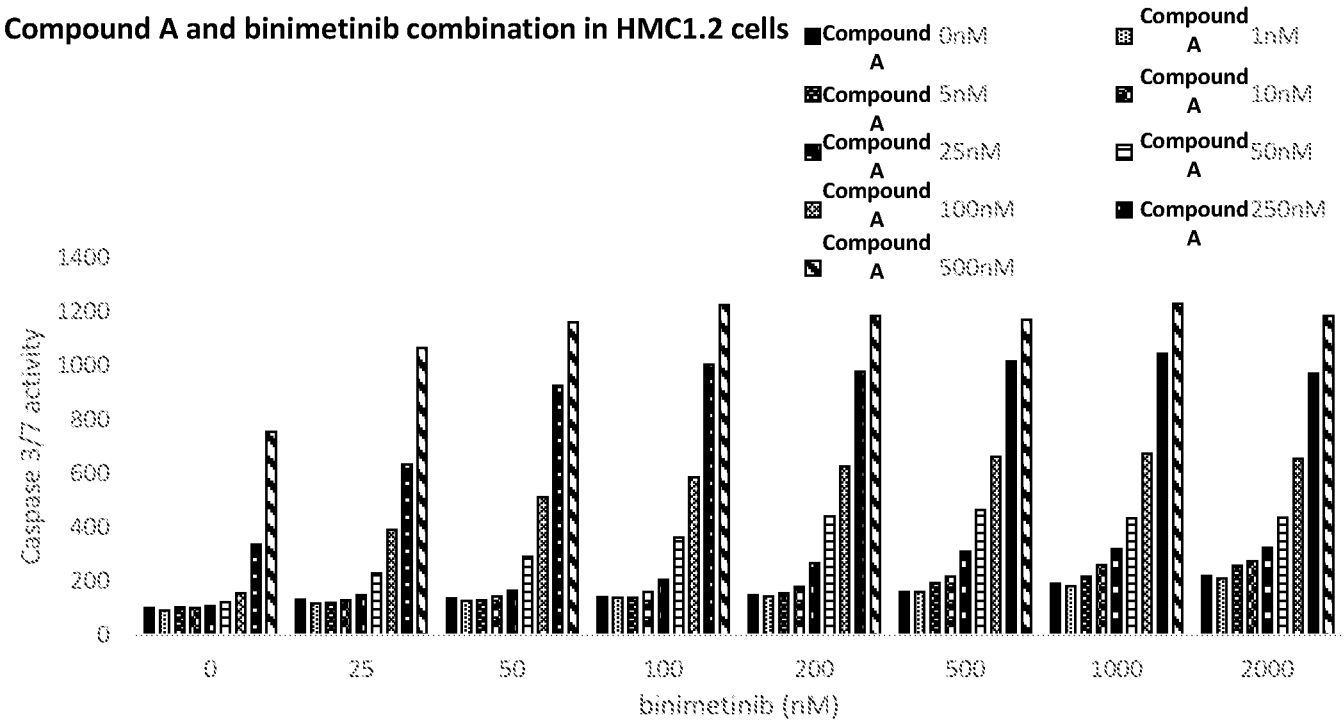

Compound A and binimetinib combination in HMC1.2 cells
Compound A 0nM
Compound A 1nM
Compound A 5nM
Compound A 10nM
Compound A 25nM
Compound A 50nM
Compound A 100nM
Compound A 250nM
Compound A 500nM
Caspase 3/7 activity
1400
1200
1000
800
600
400
200
0
0
25
50
100
200
500
1000
2000
binimetinib (nM)

Figure 4B

CI	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

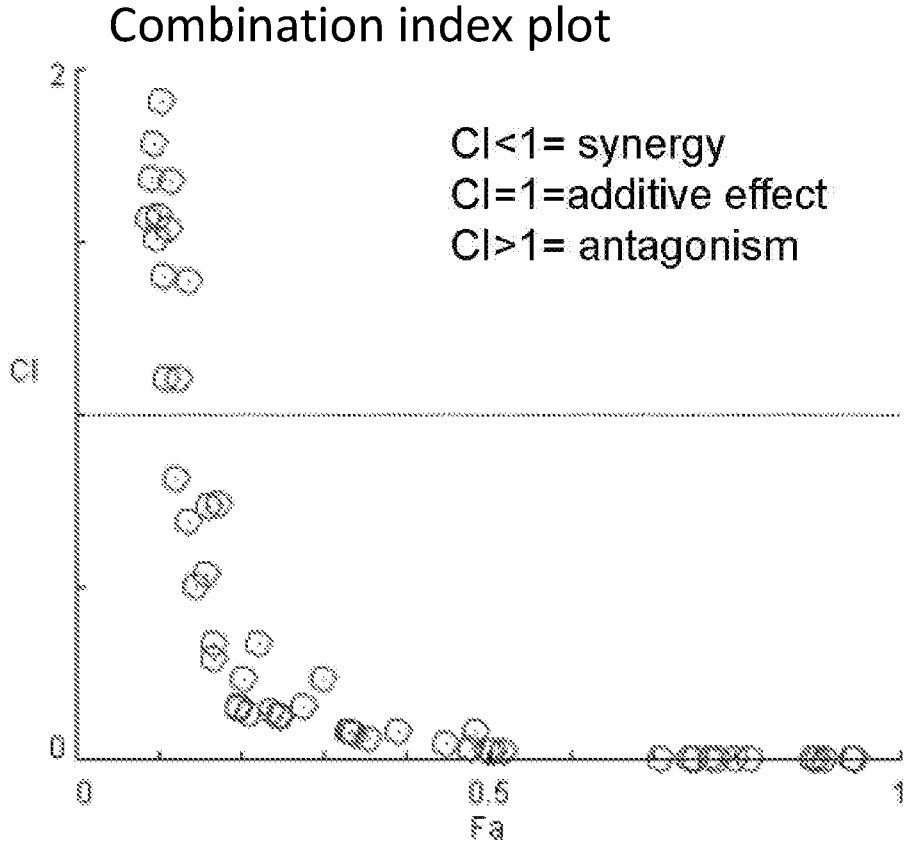

Combination index plot
CI<1= synergy
CI=1=additive effect
CI>1= antagonism
CI
2
0
0
0.5
1
Fa

Figure 5A

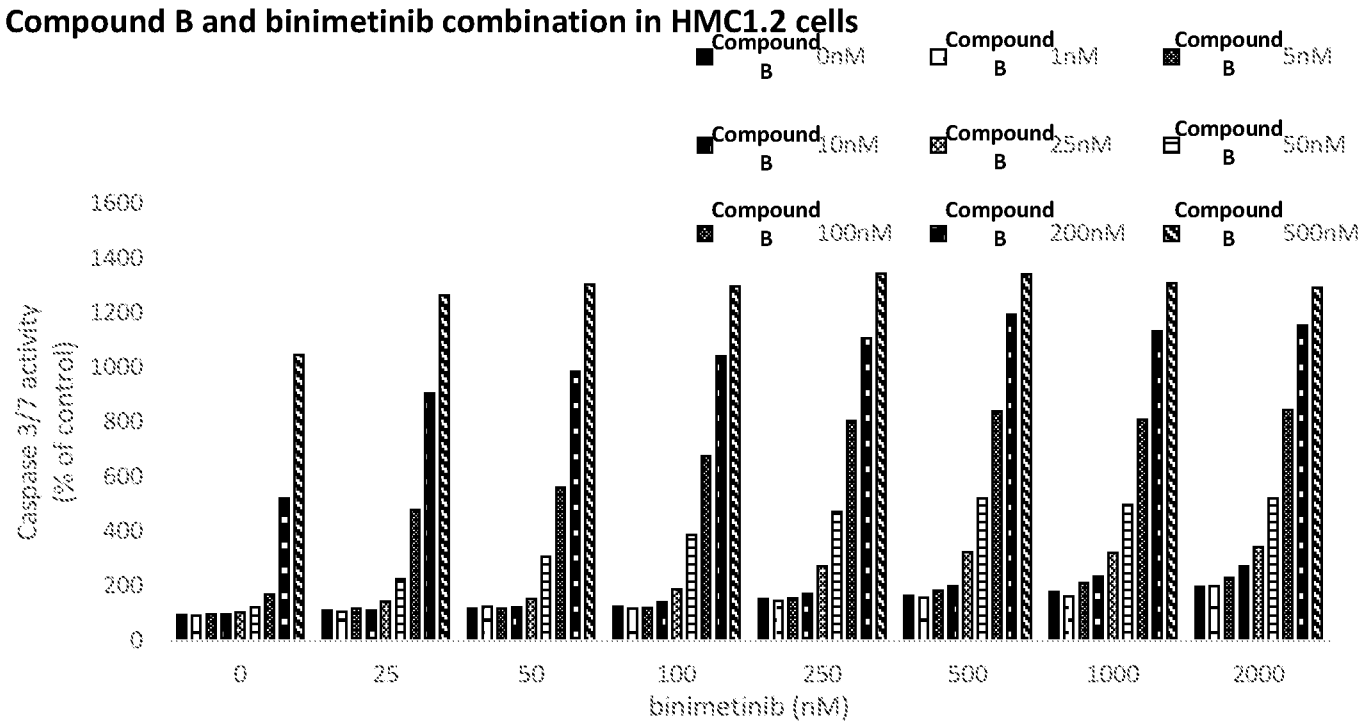

Compound B and binimetinib combination in HMC1.2 cells
Compound B 0nM
Compound B 1nM
Compound B 5nM
Compound B 10nM
Compound B 25nM
Compound B 50nM
Compound B 100nM
Compound B 200nM
Compound B 500nM
Caspase 3/7 activity (% of control)
1600
1400
1200
1000
800
600
400
200
0
0
25
50
100
250
500
1000
2000
binimetinib (nM)

Figure 5B

CI	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

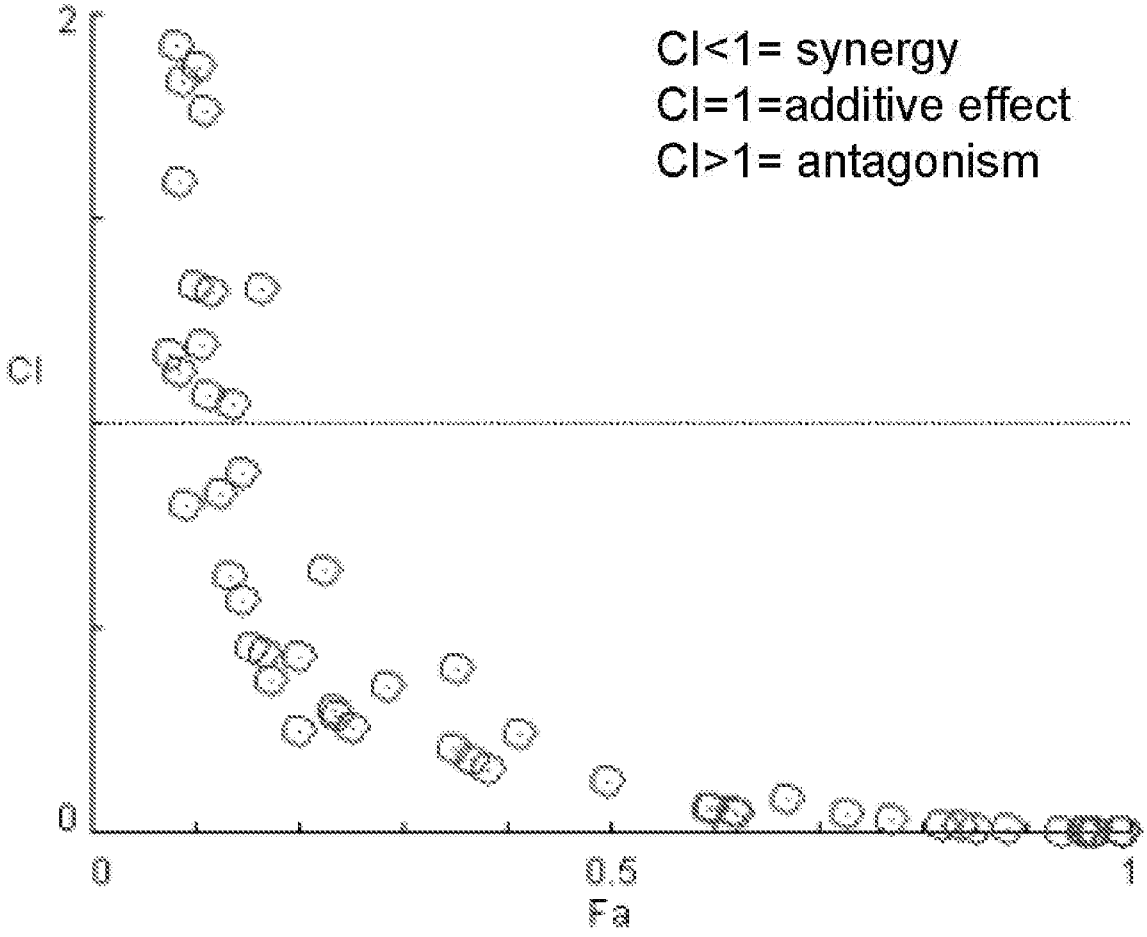


Figure 6A

Compound A and cobimetinib combination in HMC1.2 cells

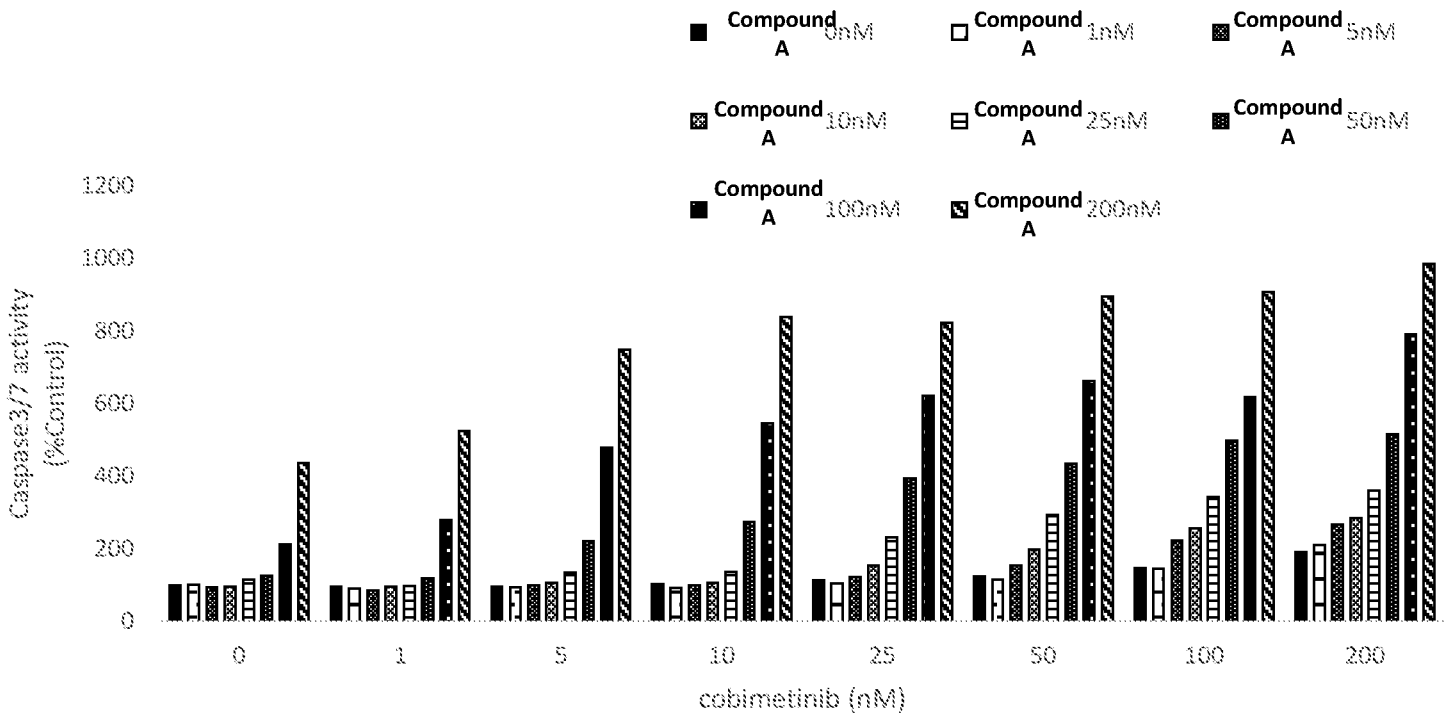


Figure 6B

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

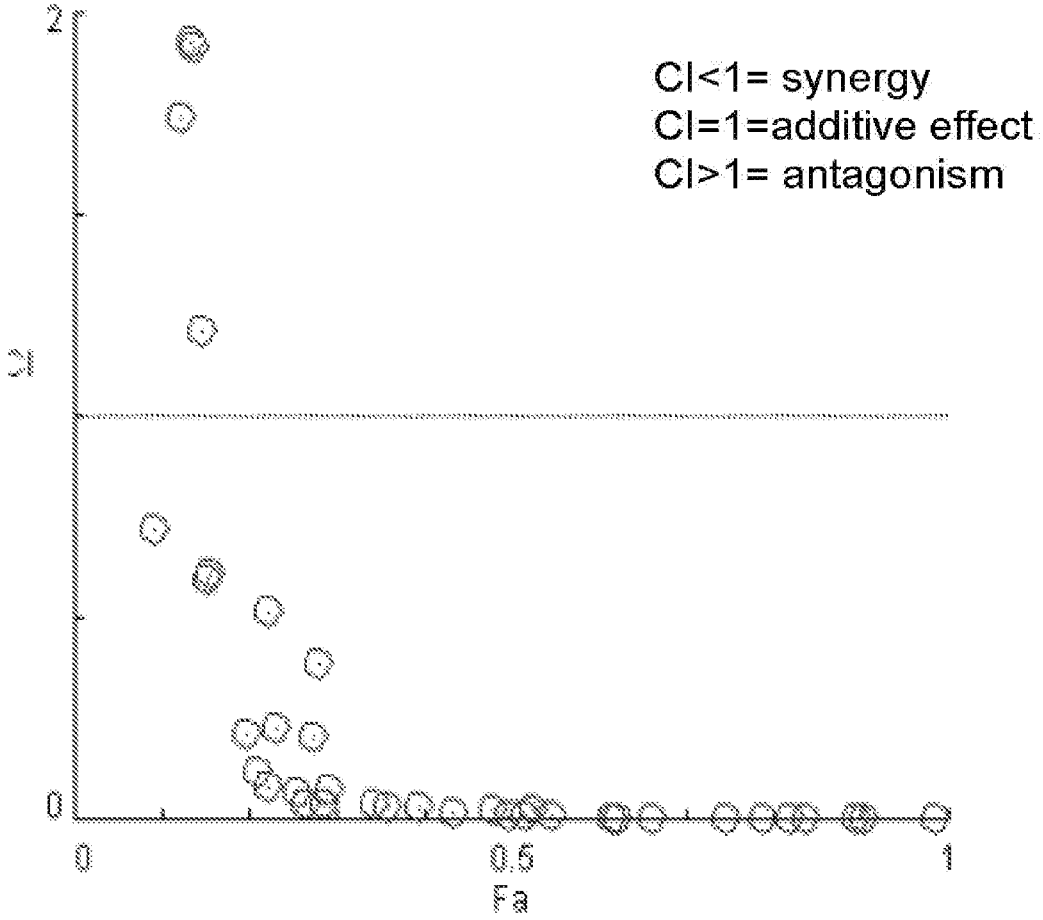


Figure 7A

Compound B and cobimetinib combination in HMC1.2 cells

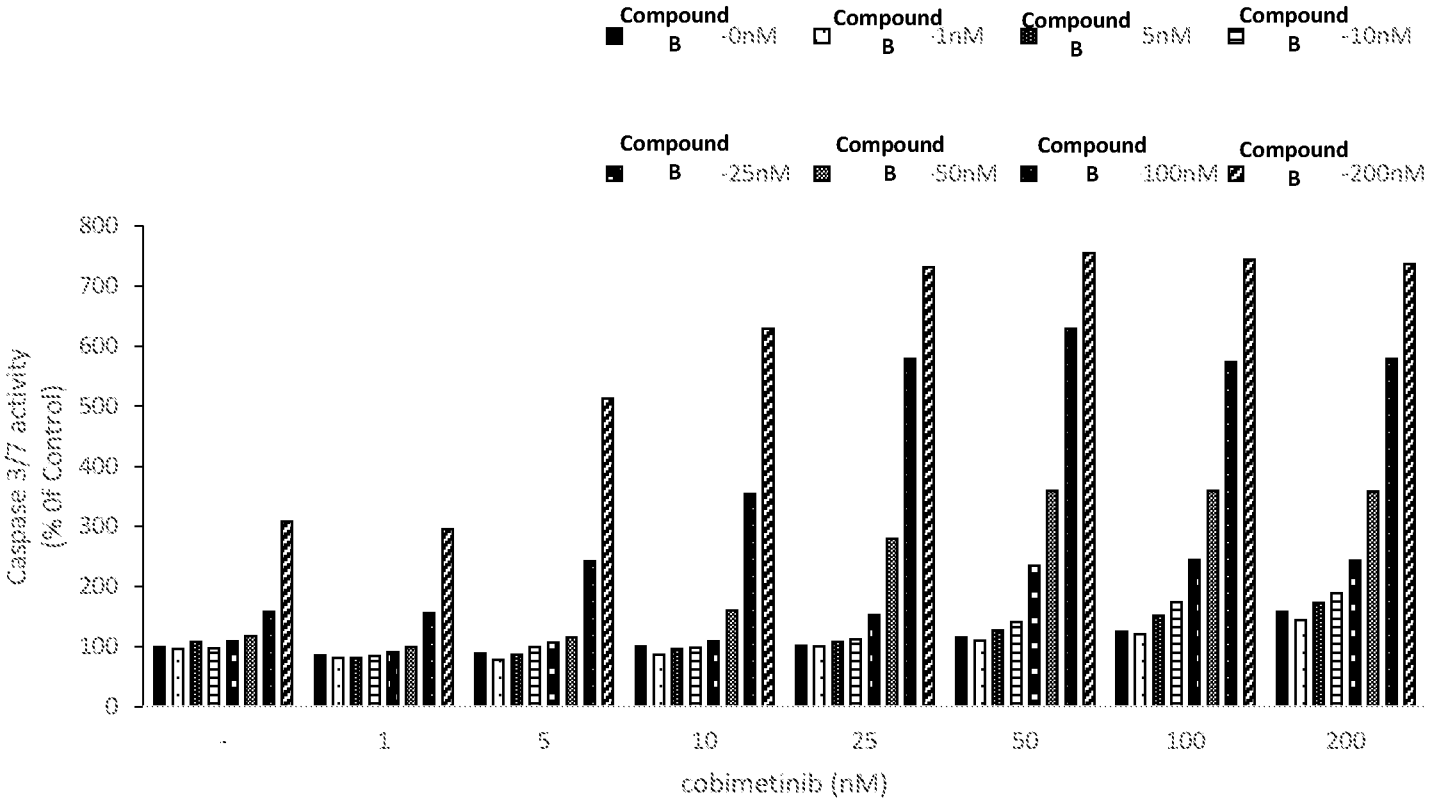


Figure 7B

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	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

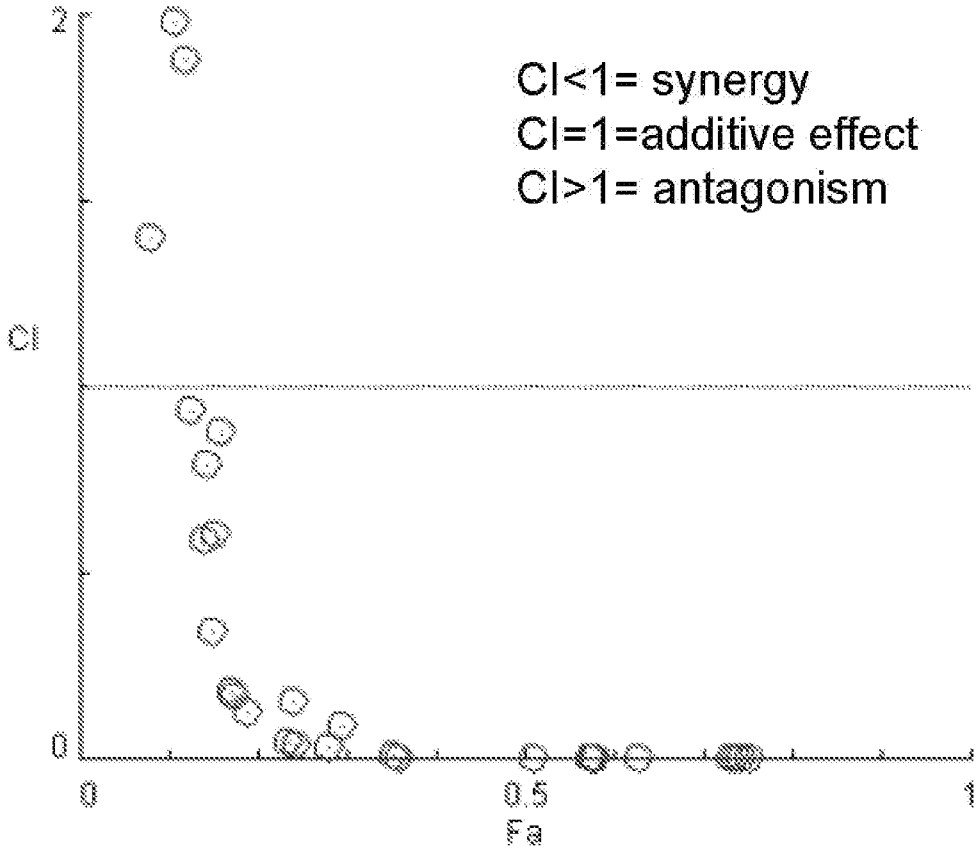


Figure 8A

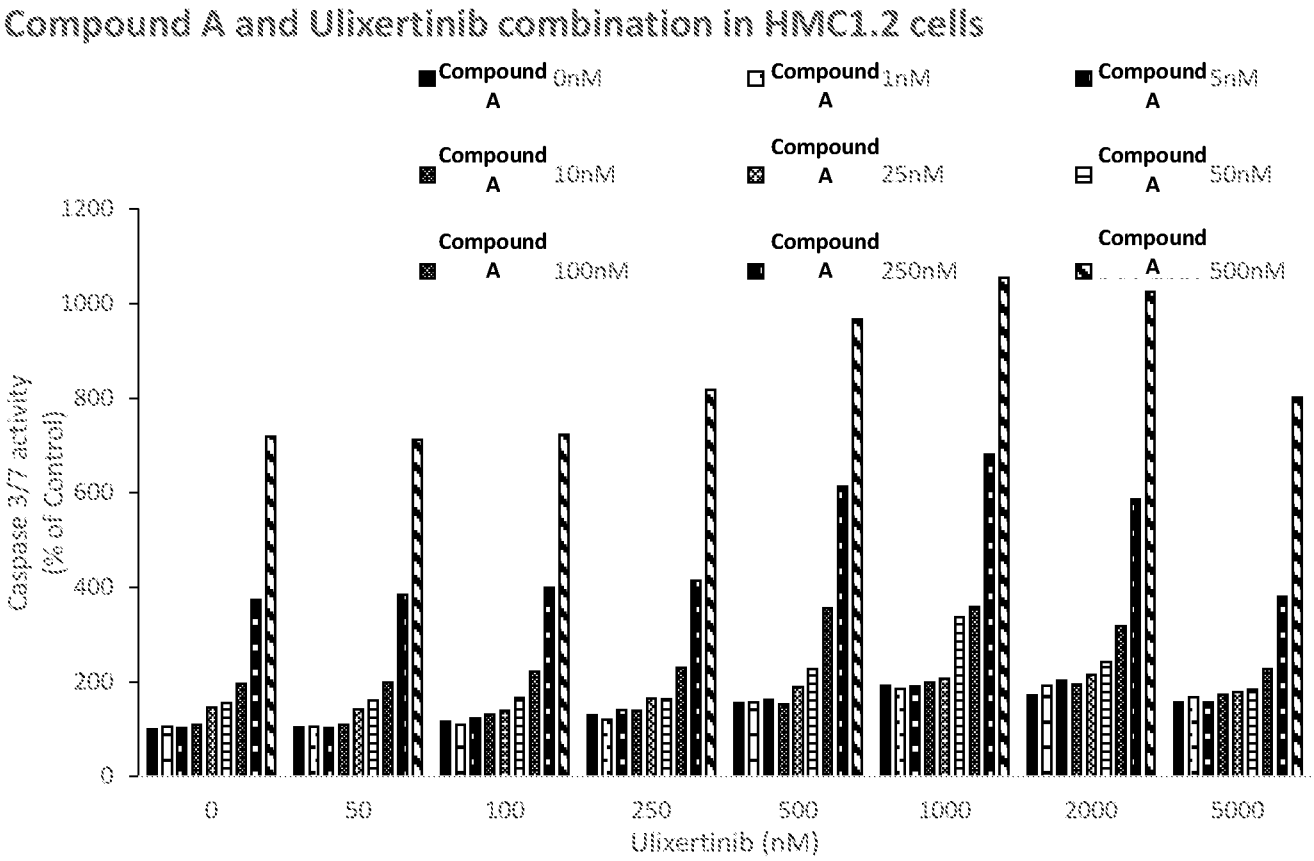

Compound A and Ulixertinib combination in HMC1.2 cells
Compound A 0nM
Compound A 1nM
Compound A 5nM
Compound A 10nM
Compound A 25nM
Compound A 50nM
Compound A 100nM
Compound A 250nM
Compound A 500nM
Caspase 3/7 activity (% of Control)
1200
1000
800
600
400
200
0
0
50
100
250
500
1000
2000
5000
Ulixertinib (nM)

Figure 8B

CI	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

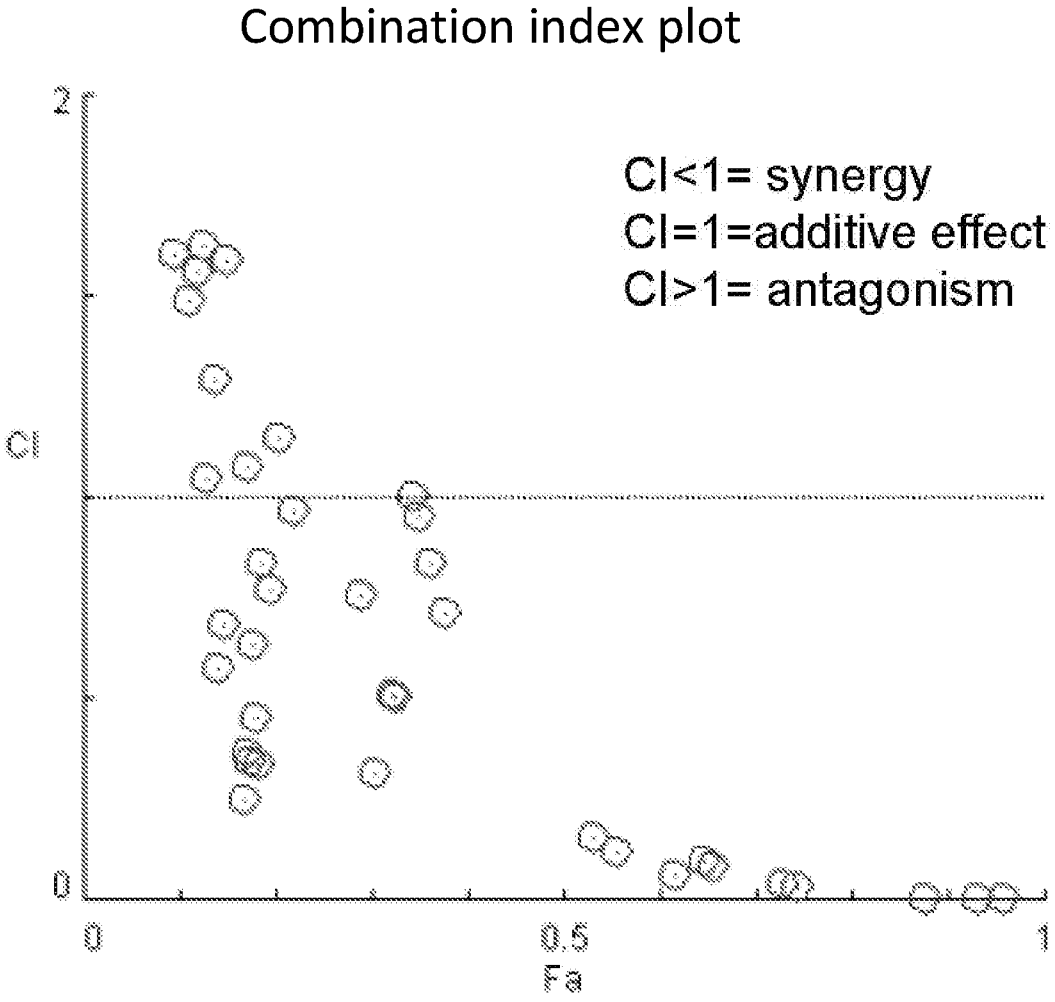

Combination index plot
CI<1= synergy
CI=1=additive effect
CI>1= antagonism
CI
2
0
0
0.5
1
Fa

Figure 9A

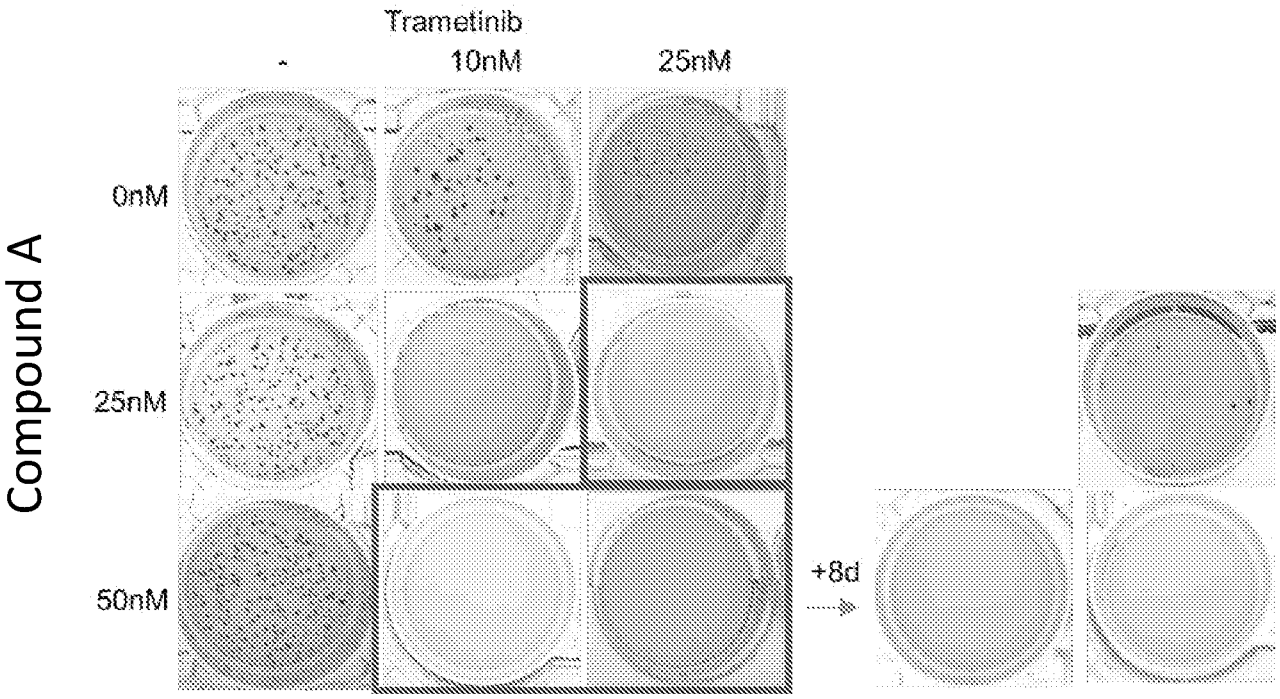


Figure 9B

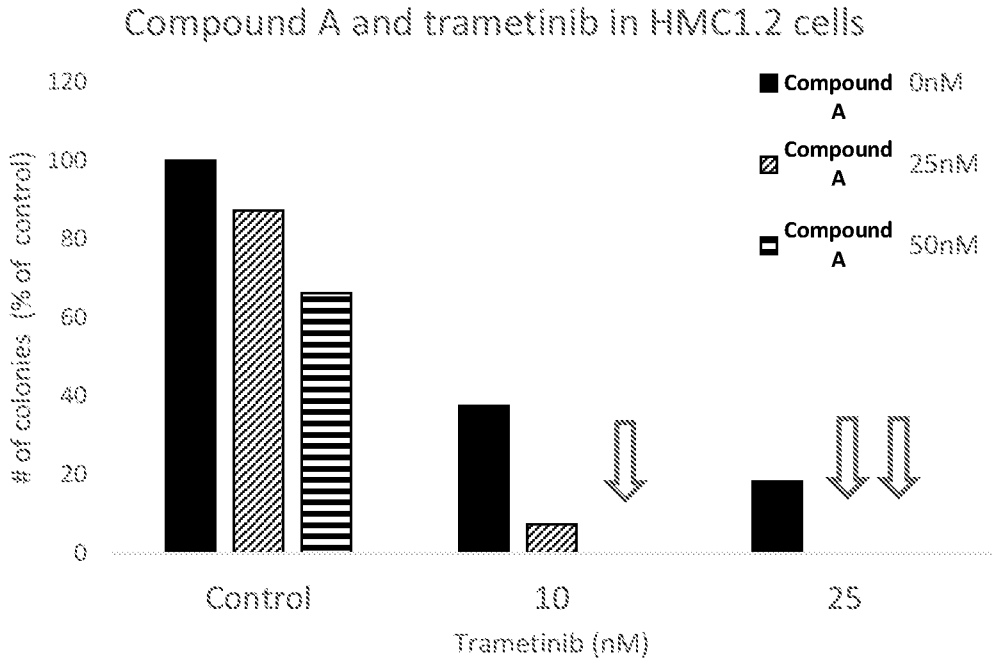


Figure 10A

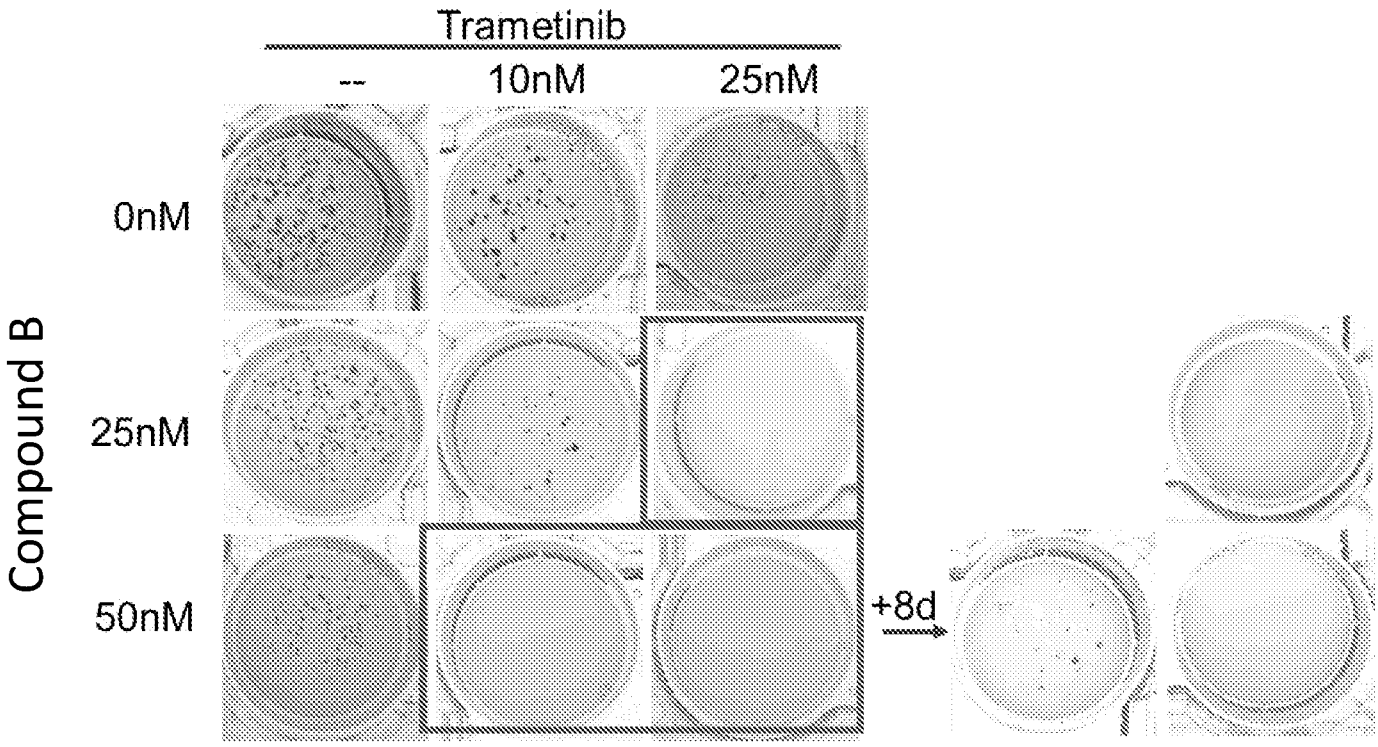


Figure 10B

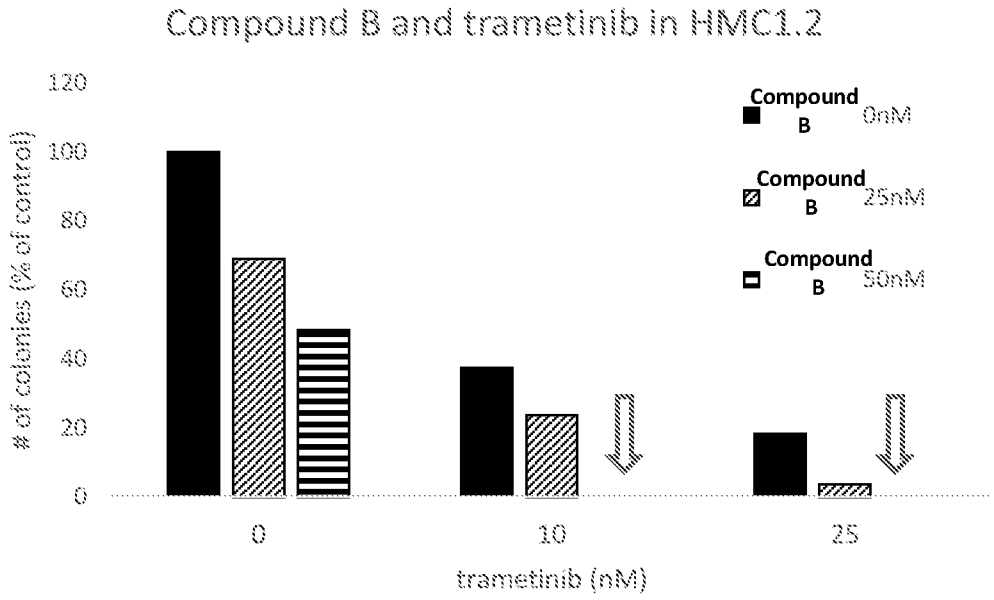


Figure 11A

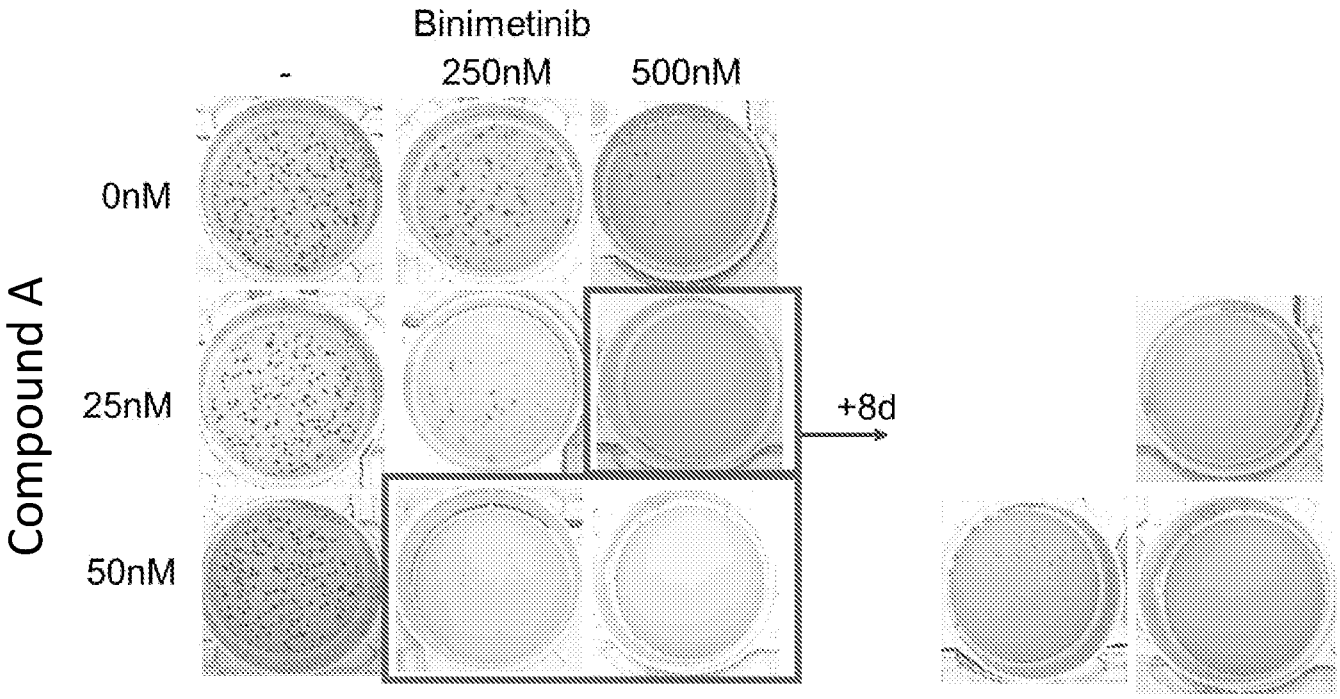


Figure 11B

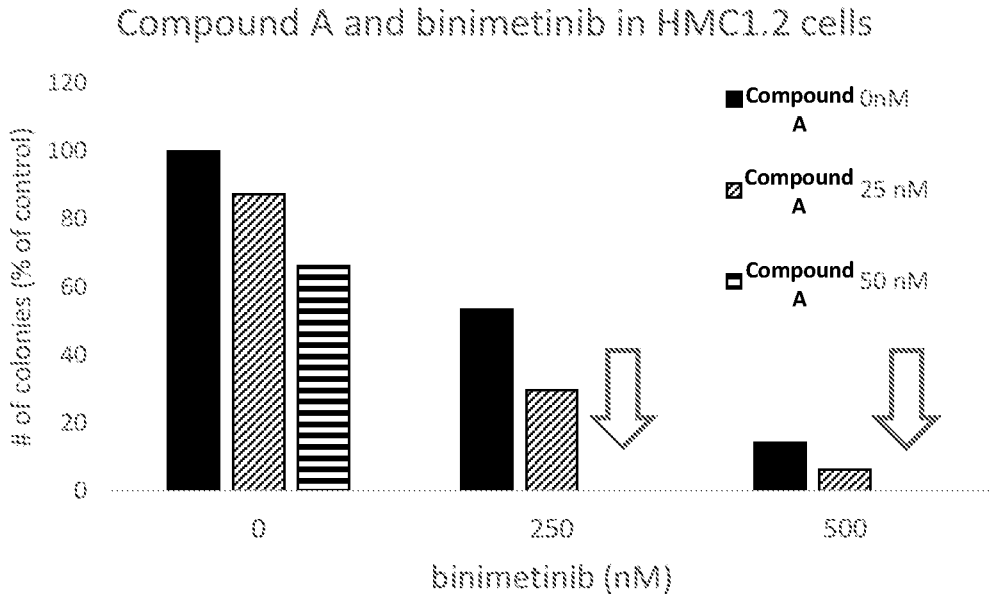


Figure 12A

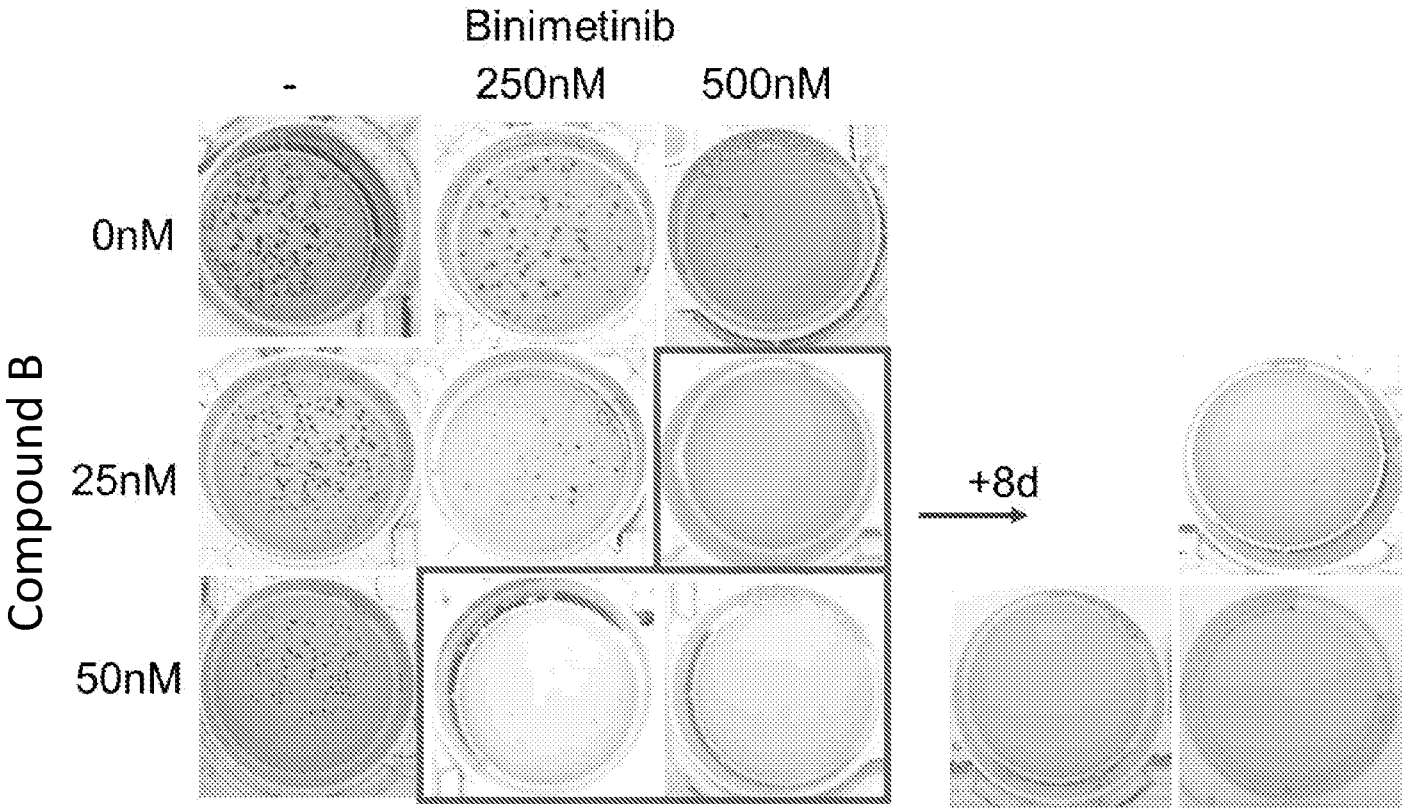


Figure 12B

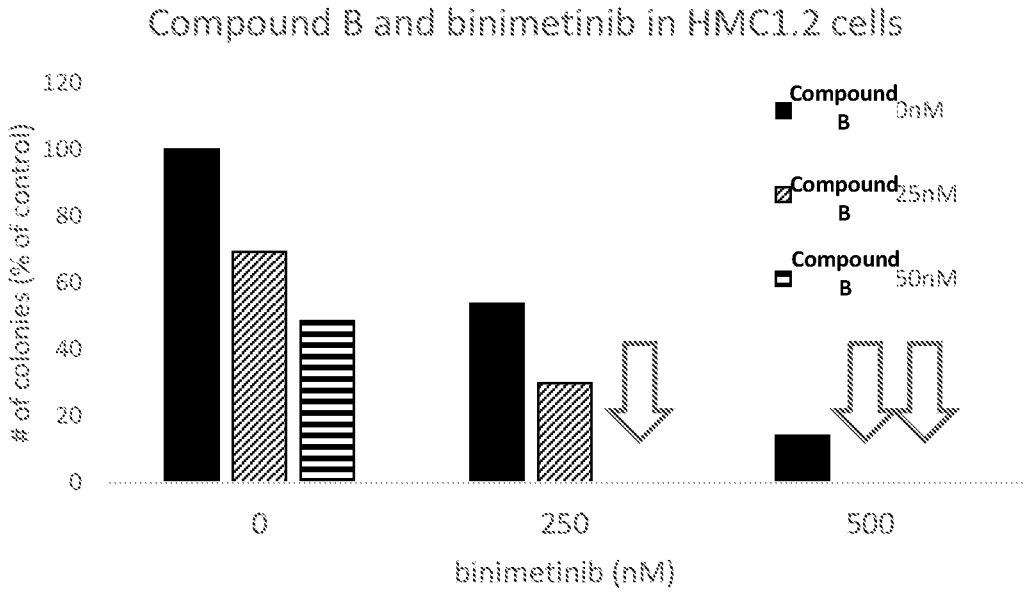


Figure 13A

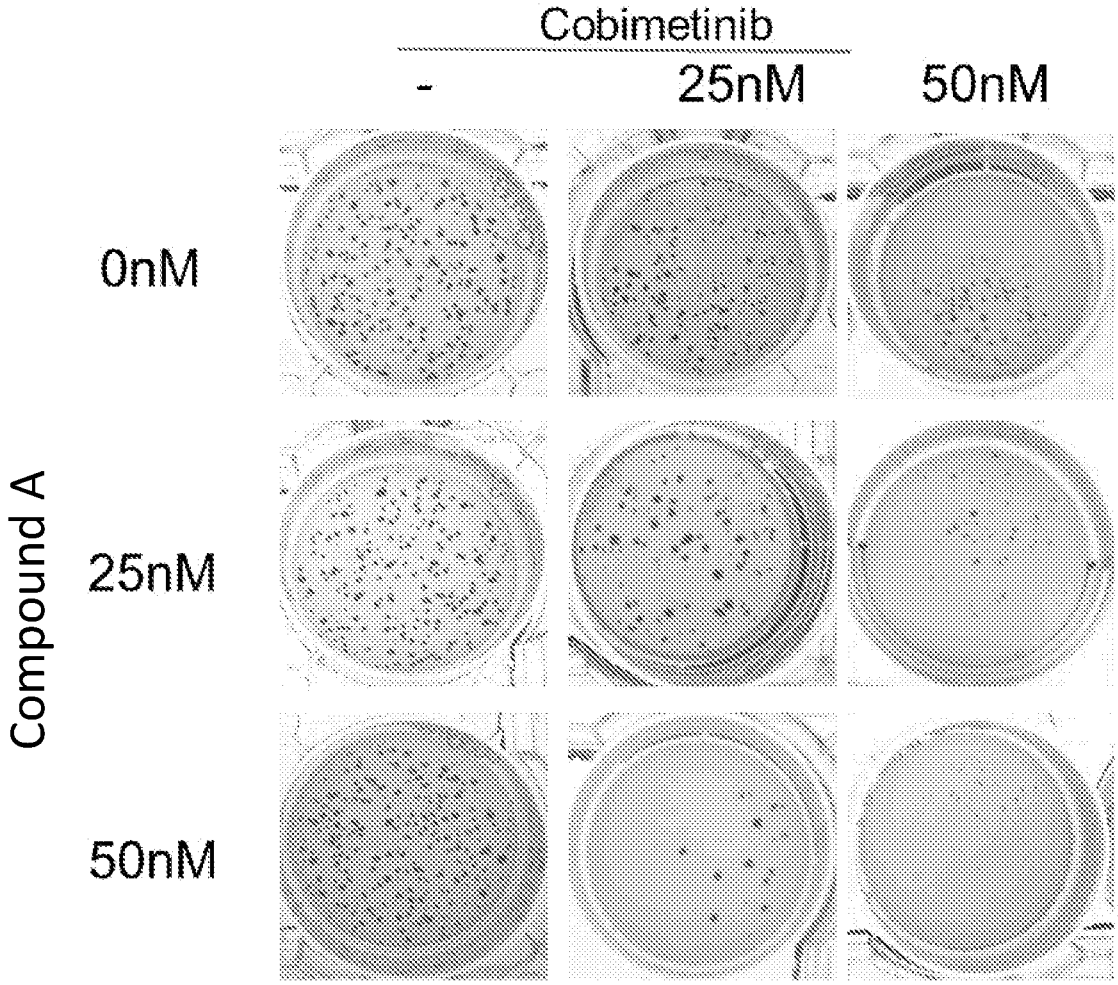


Figure 13B

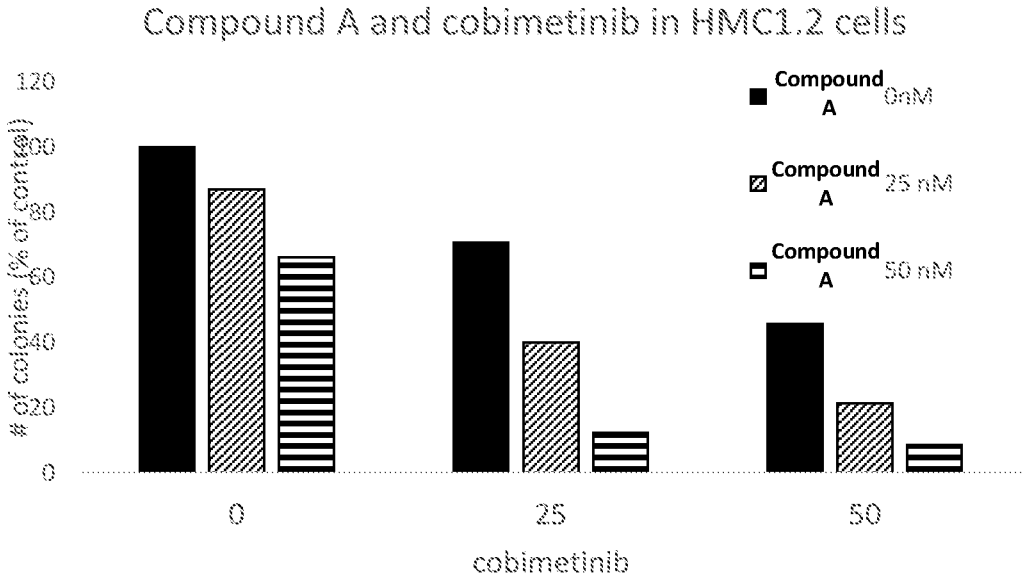


Figure 14A

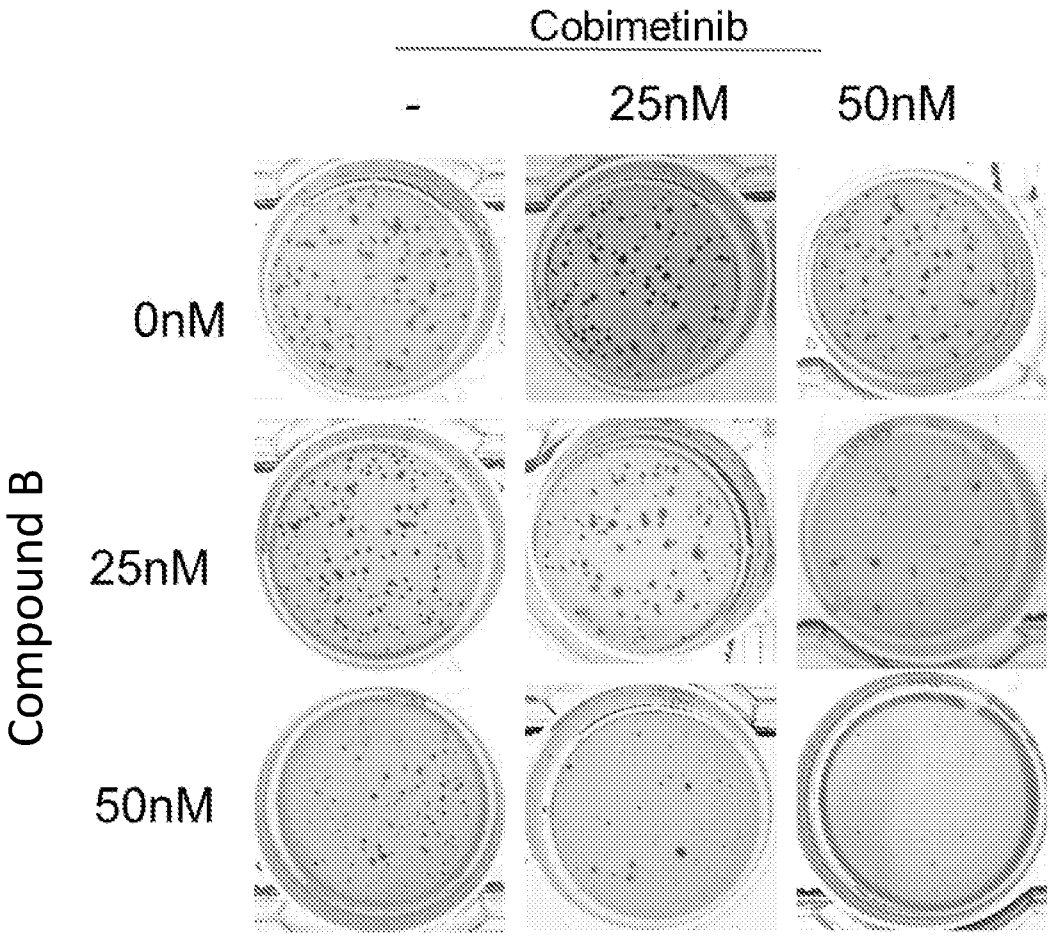


Figure 14B

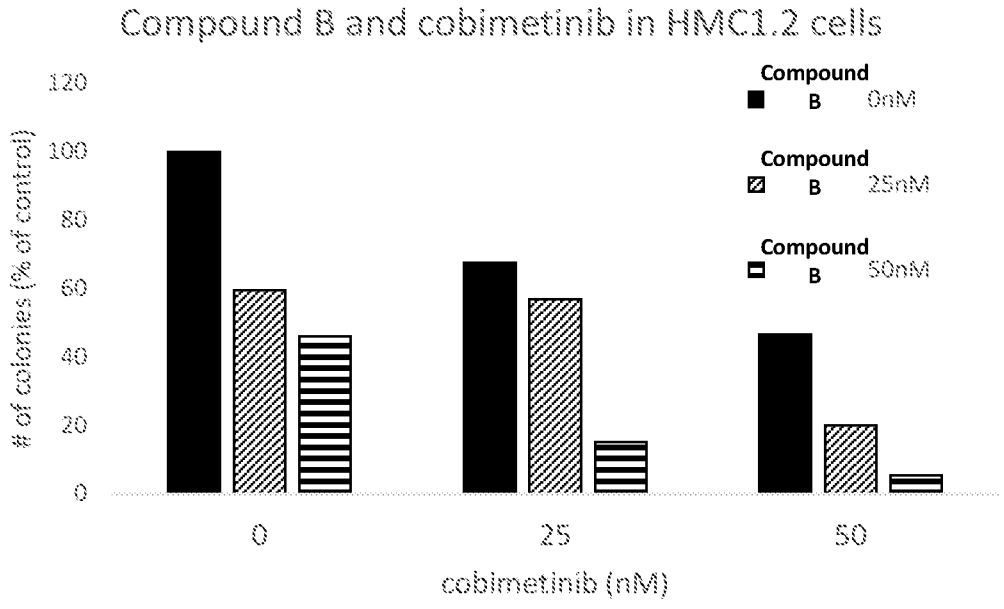


Figure 15A

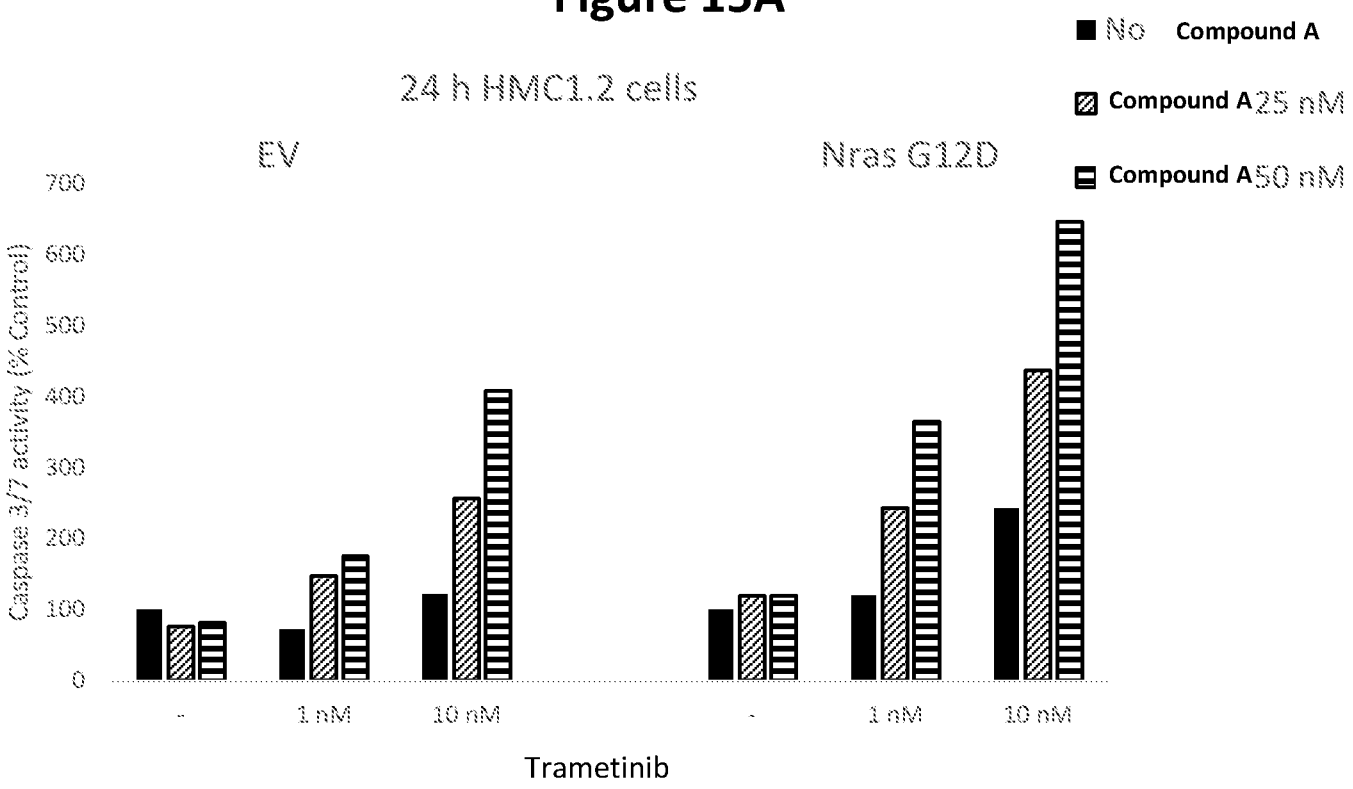


Figure 15B

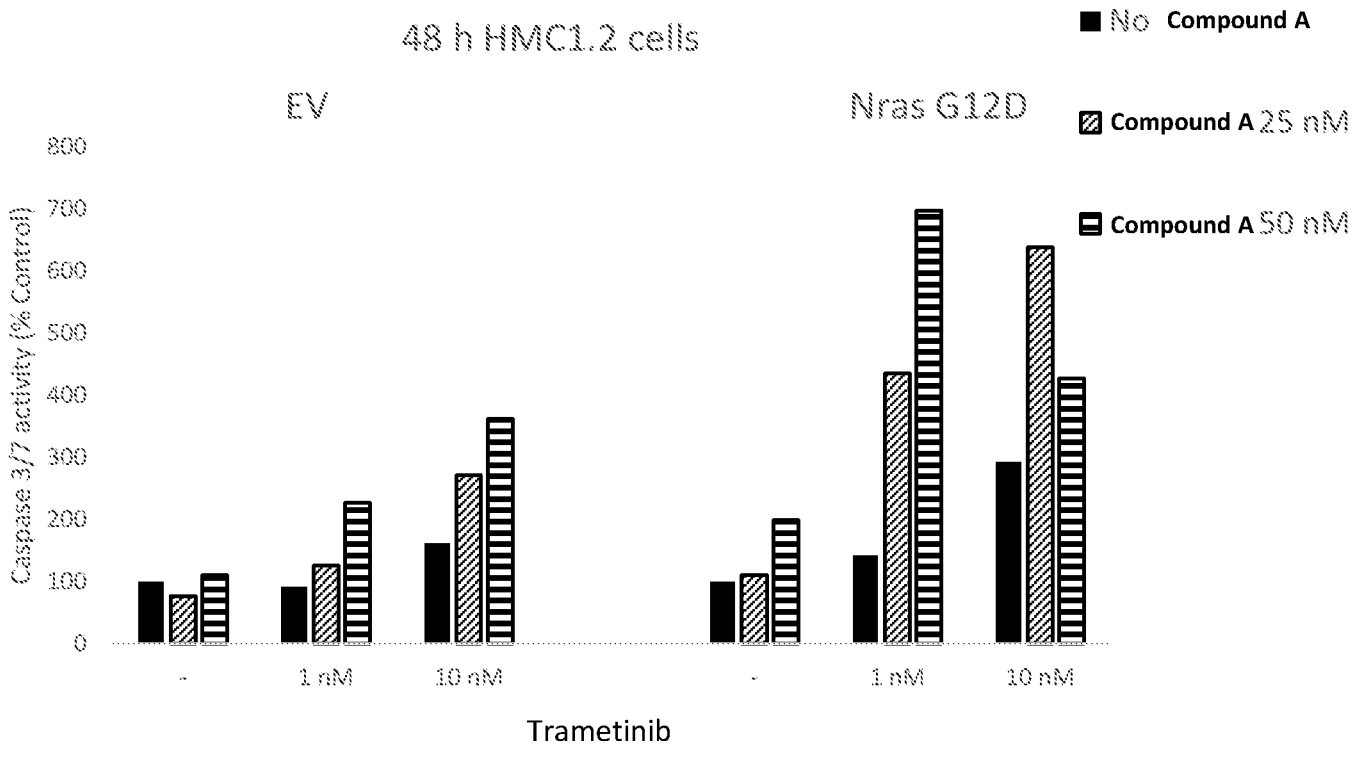


Figure 16A

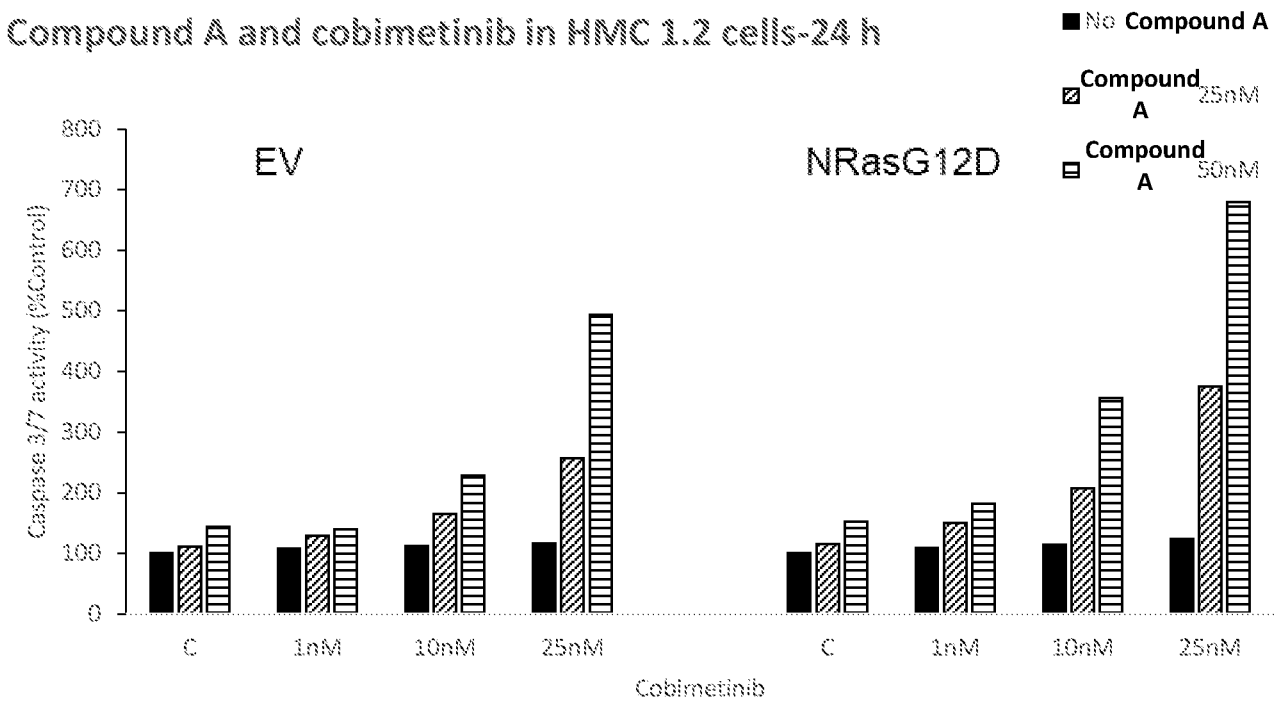


Figure 16B

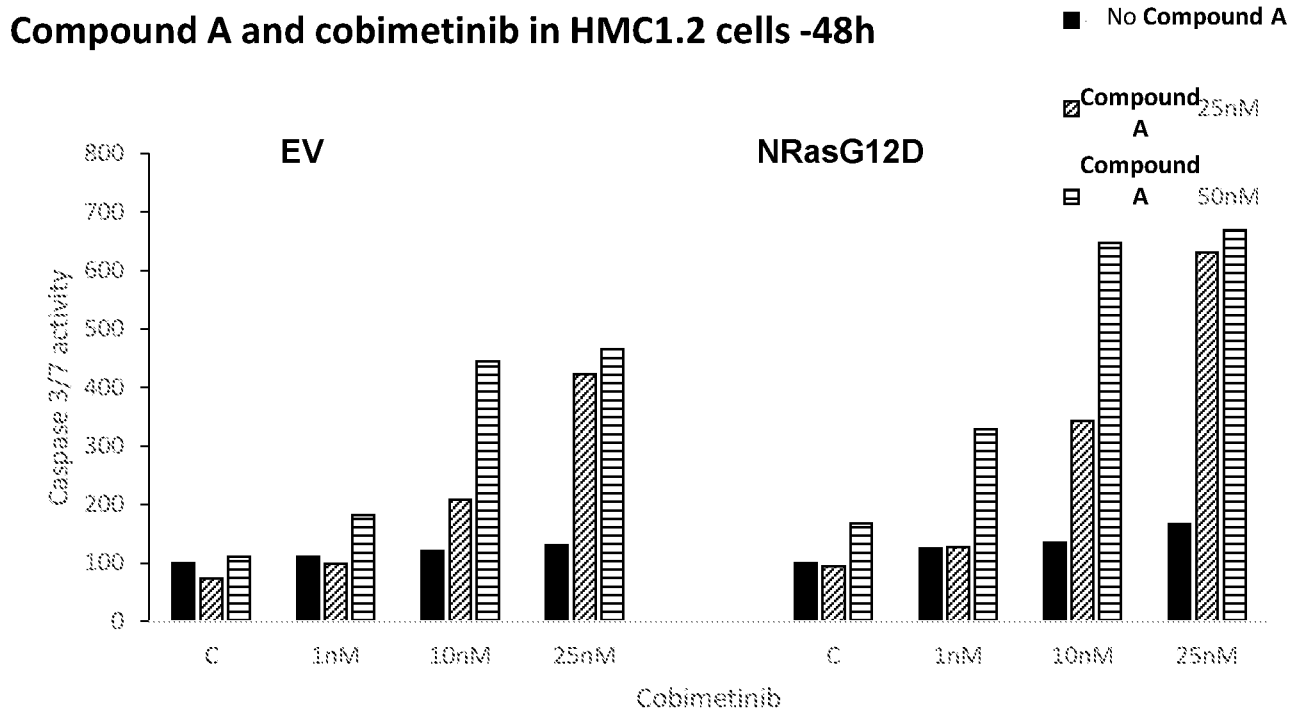


Figure 17A

HMC1.2-EV cells

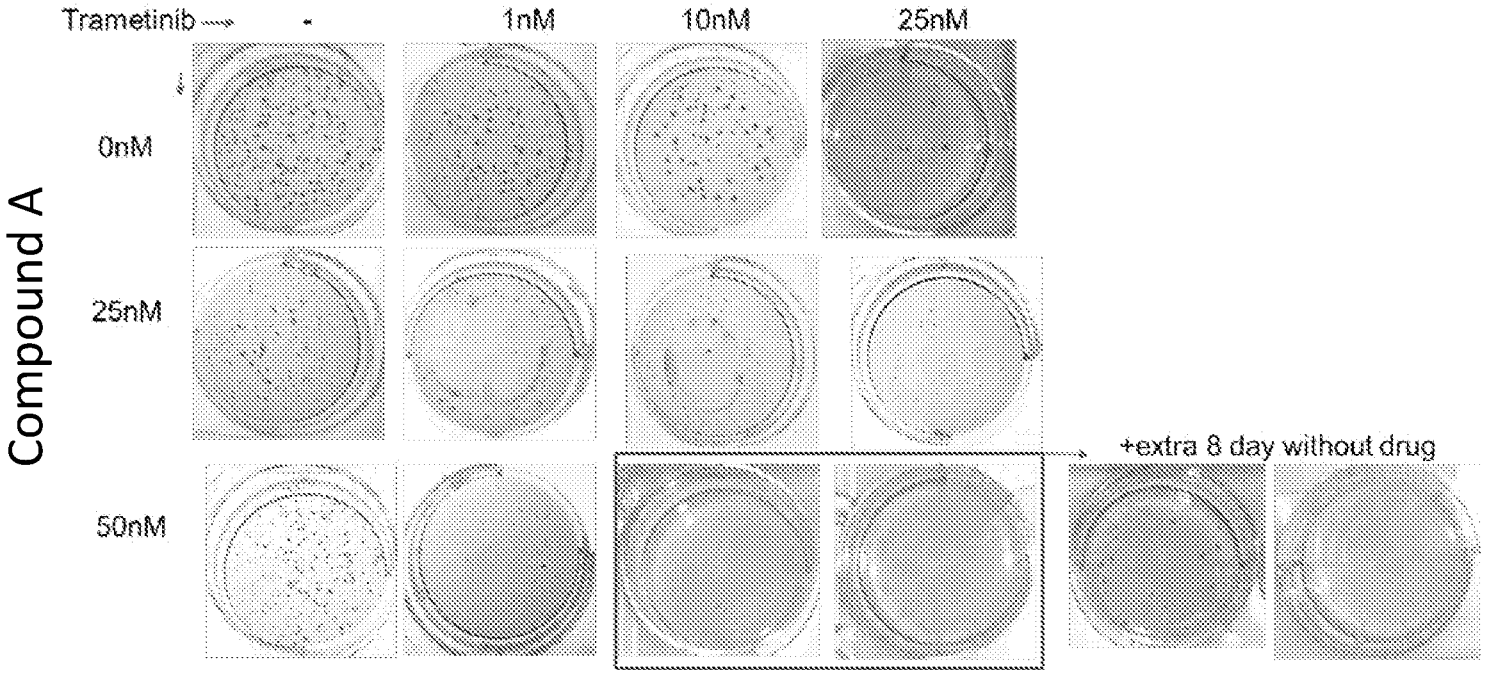


Figure 17B

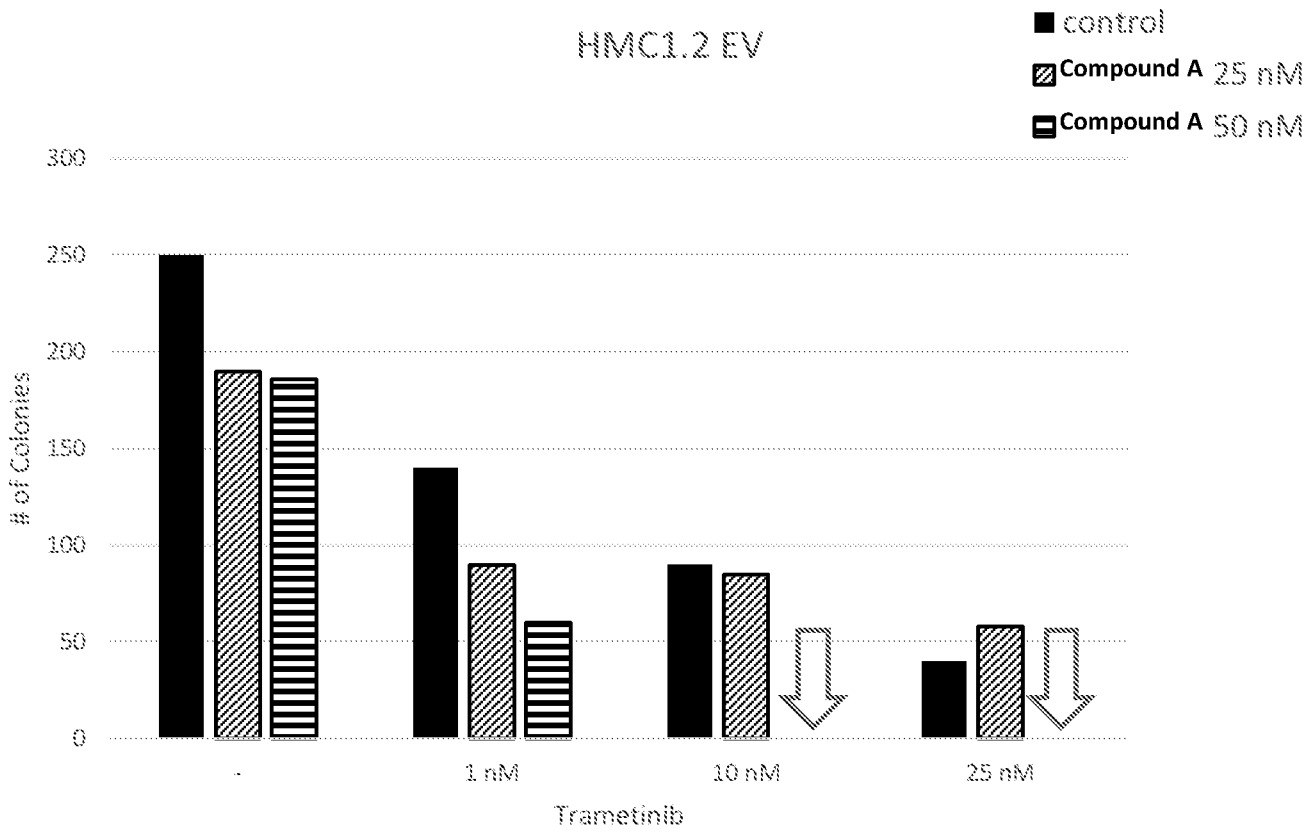


Figure 17C

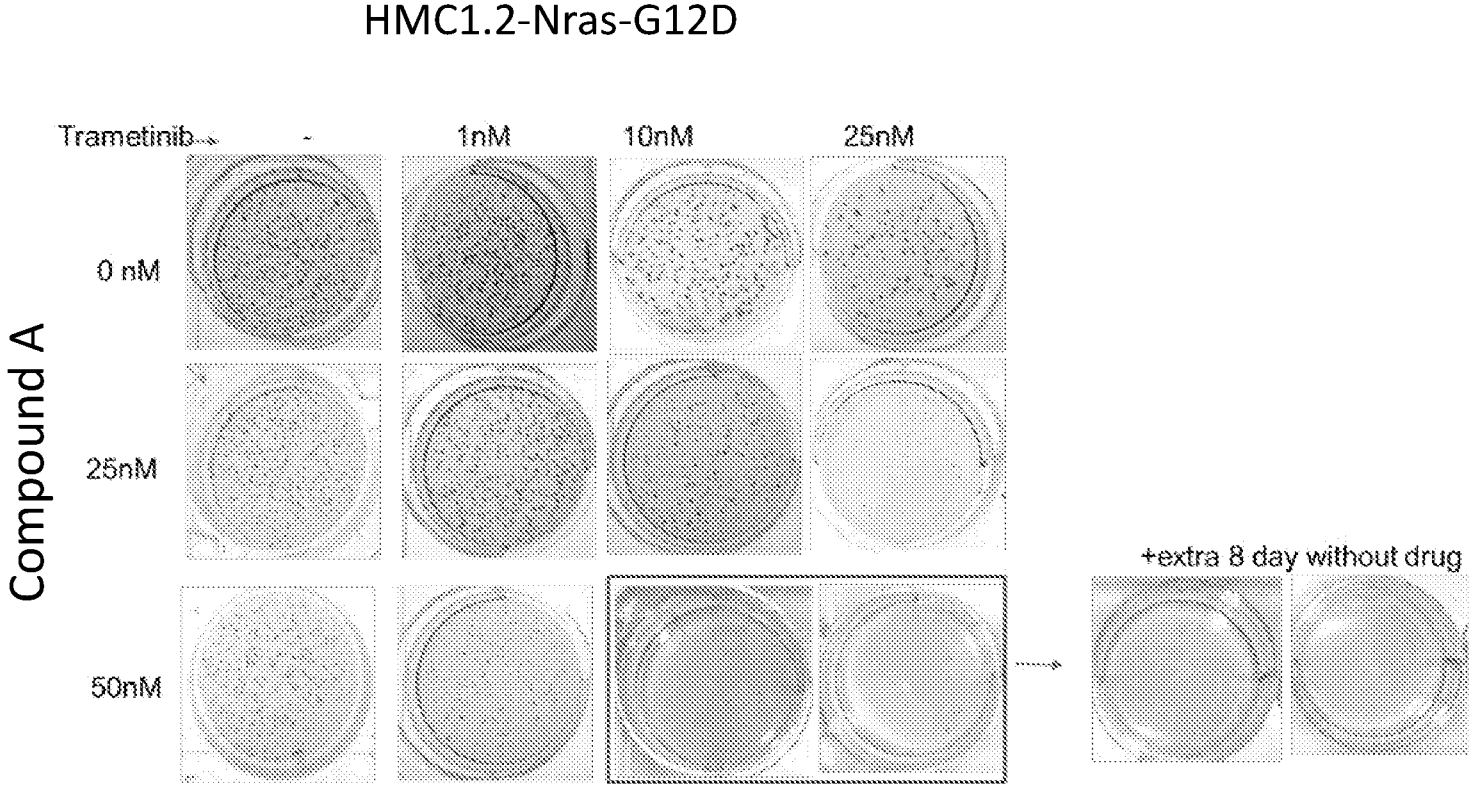


Figure 17D

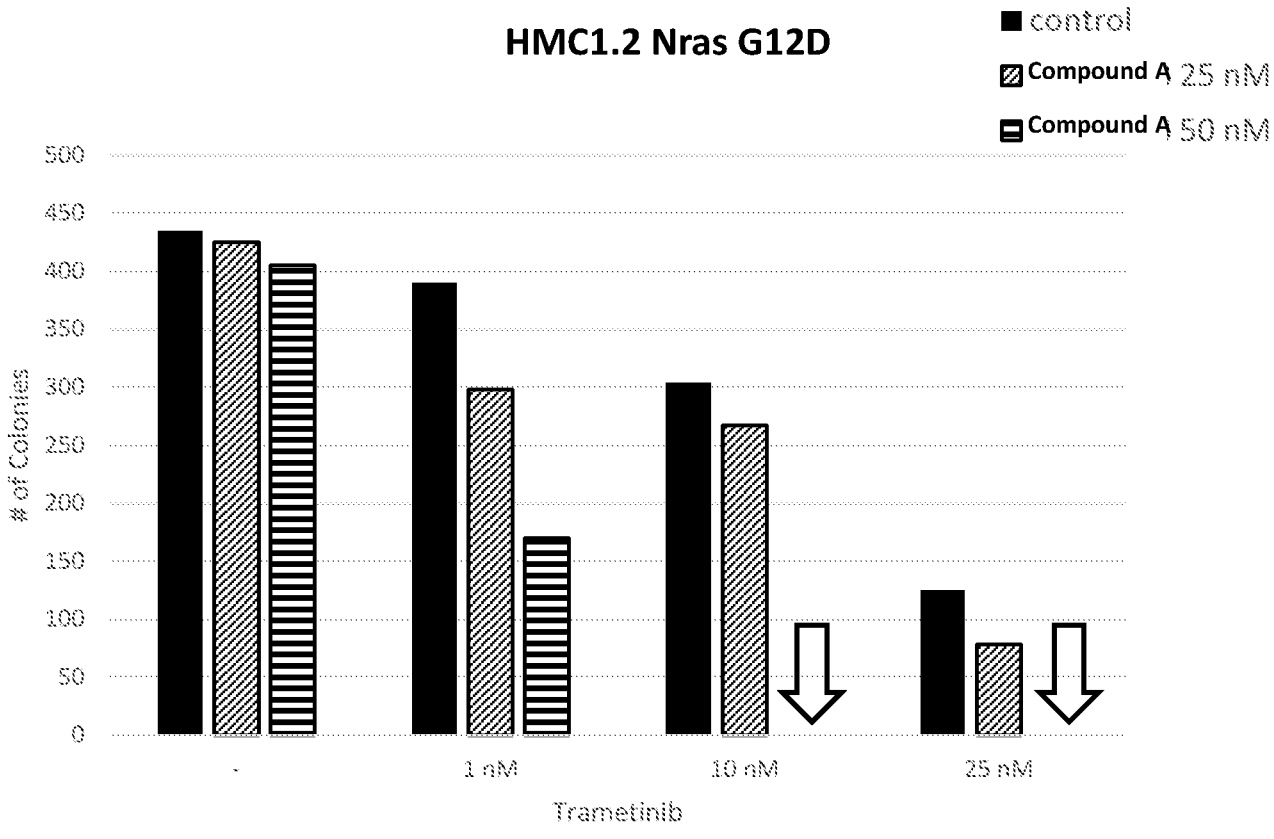


Figure 18A

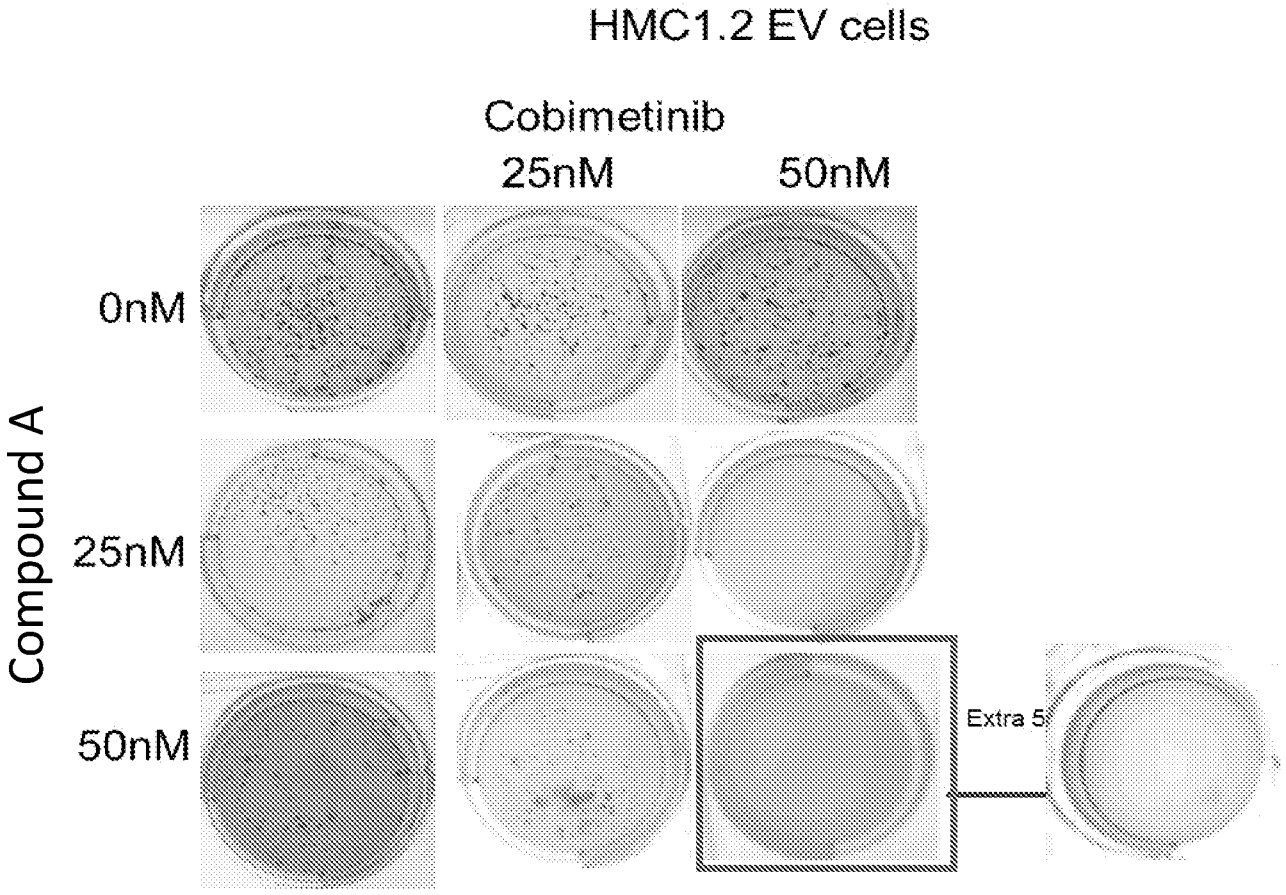


Figure 18B

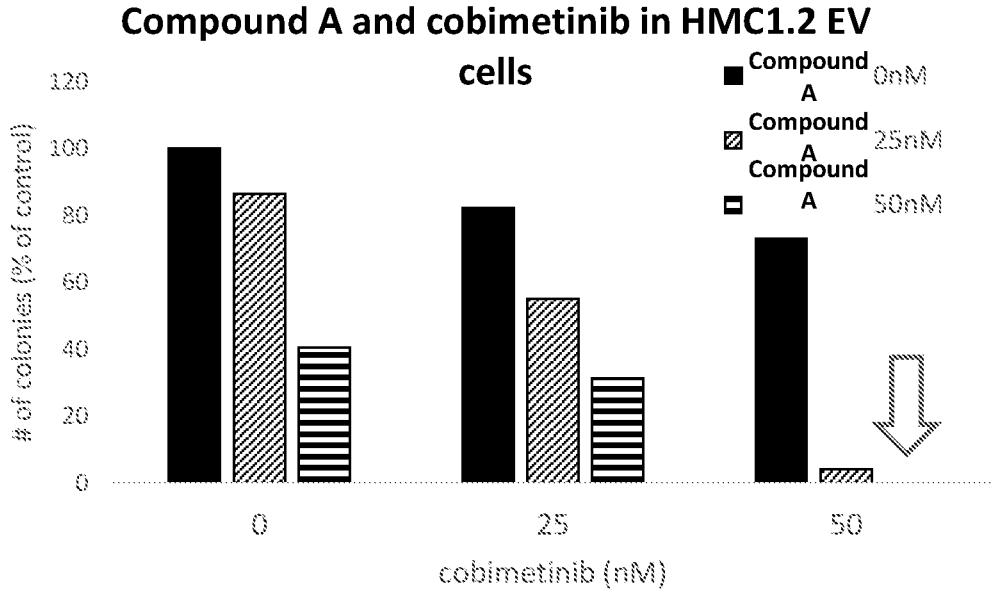


Figure 18C

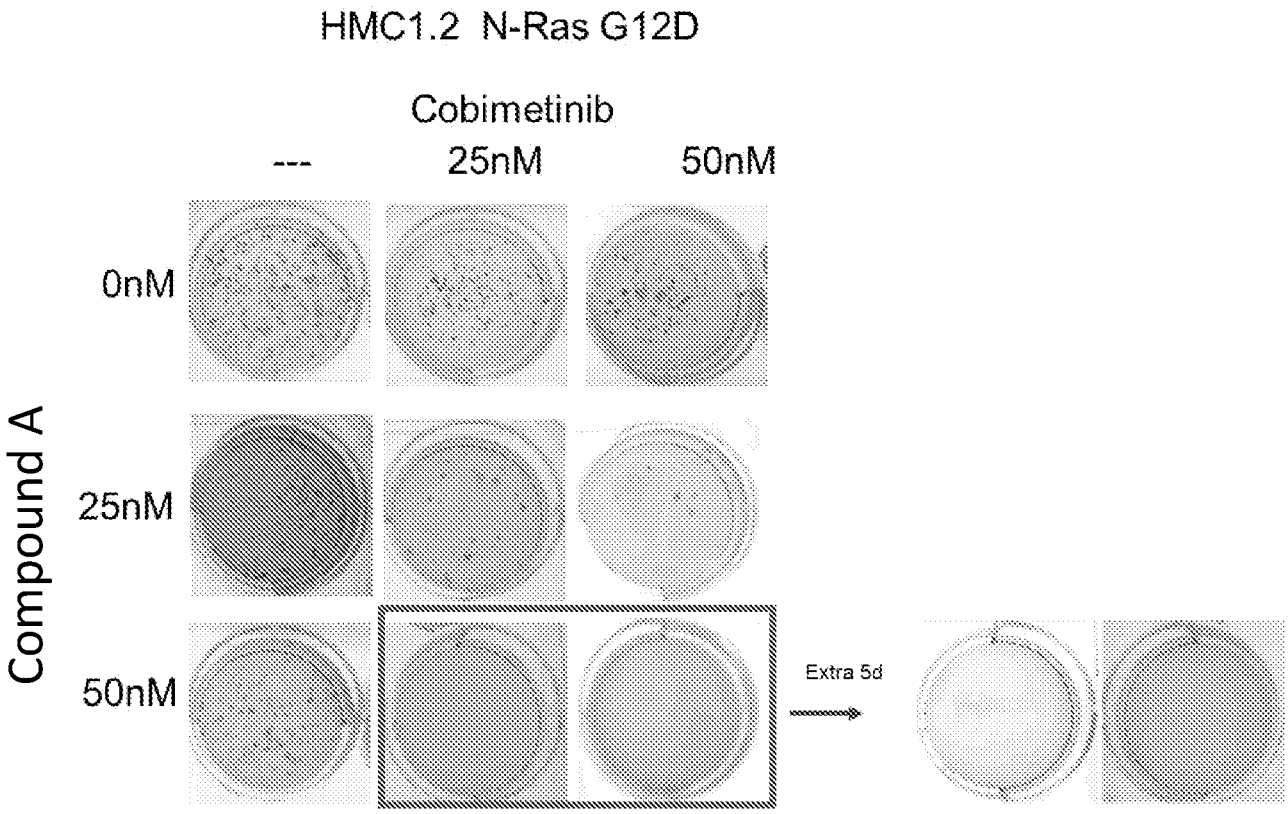


Figure 18D

