Figure 1

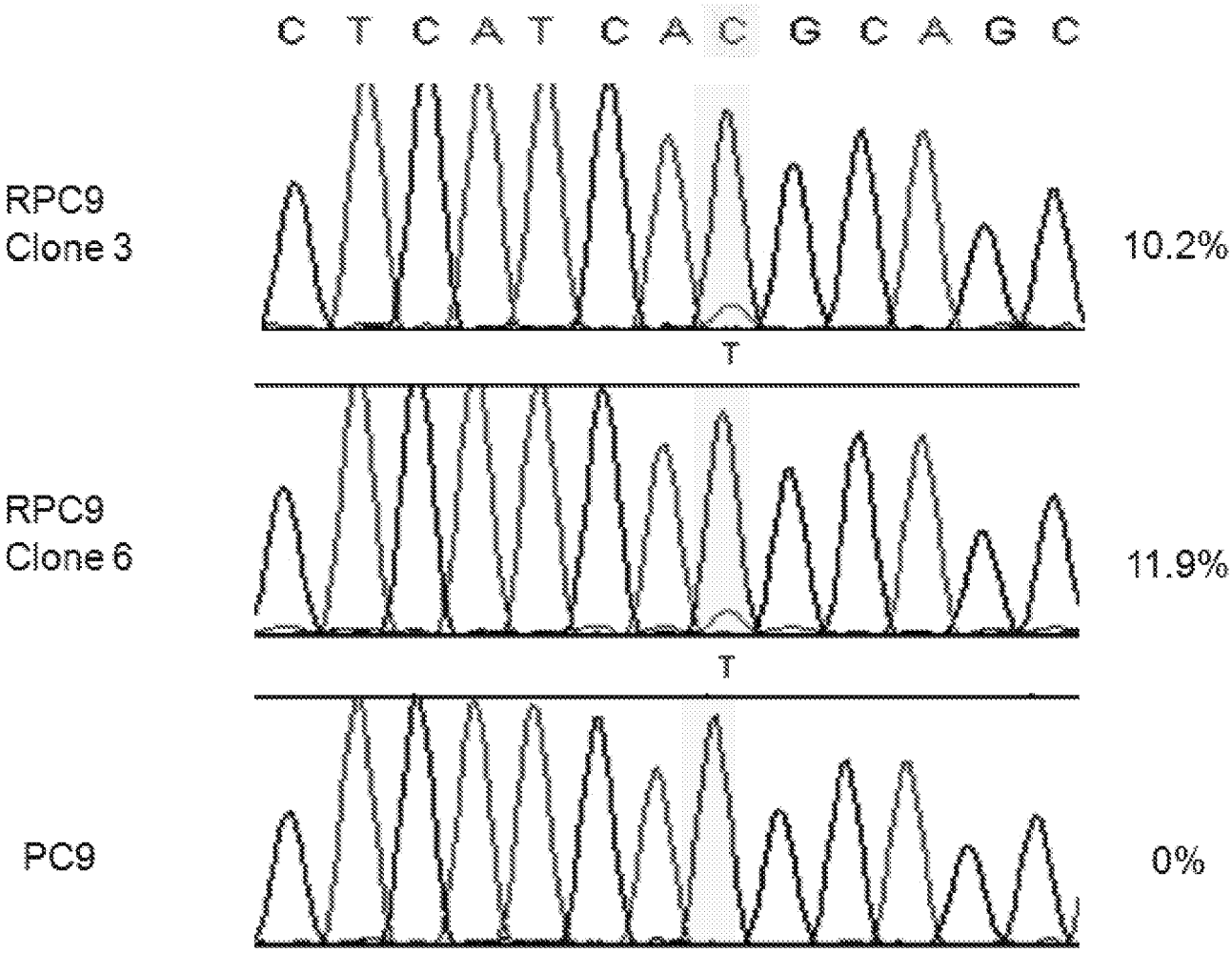
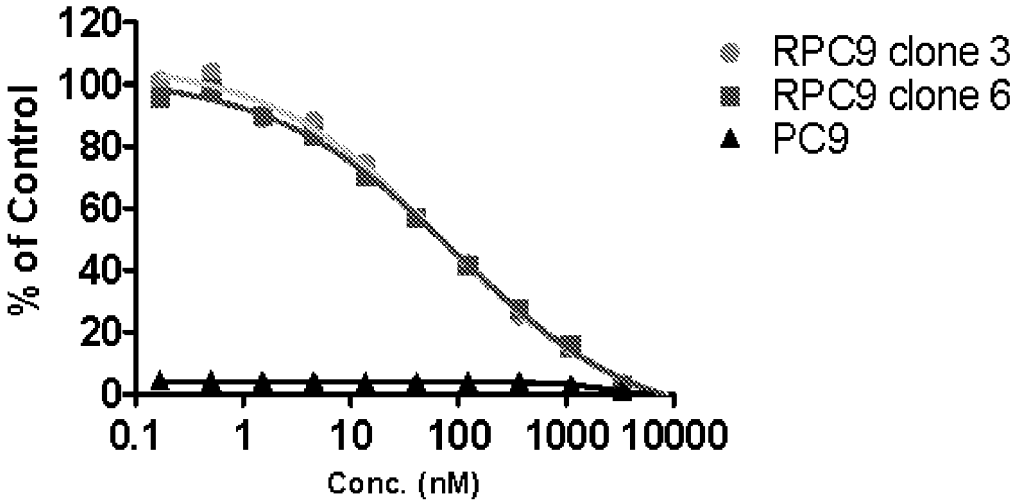


Figure 2

A

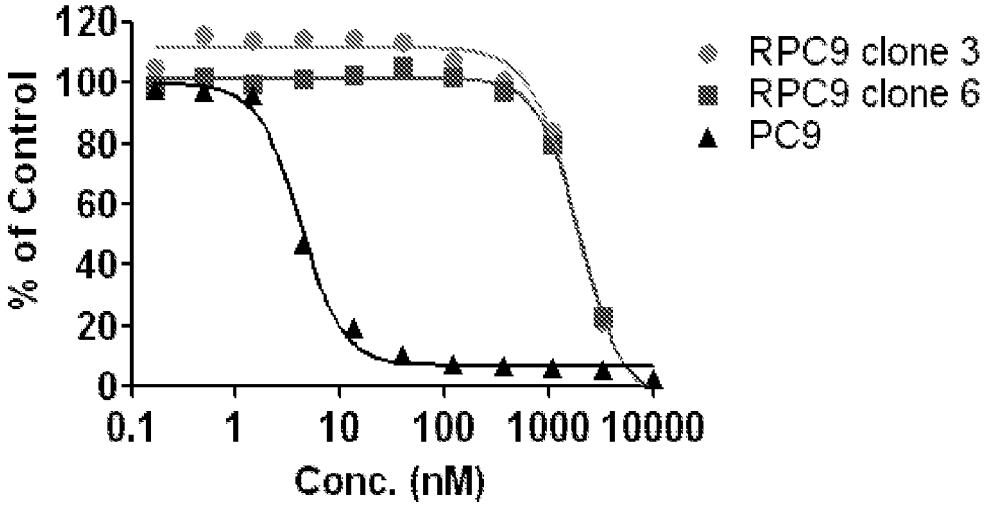


IC_{50} PC9<0.2 nM

IC_{50} RPC9 clone 3=73 nM

IC_{50} RPC9 clone 6=64 nM

B



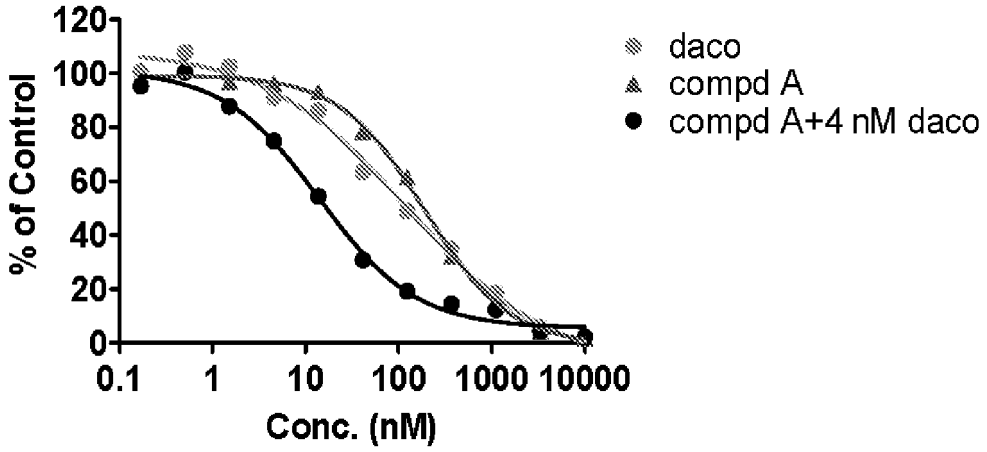
IC_{50} PC9=8.34 nM

IC_{50} RPC9 clone 3=2314 nM

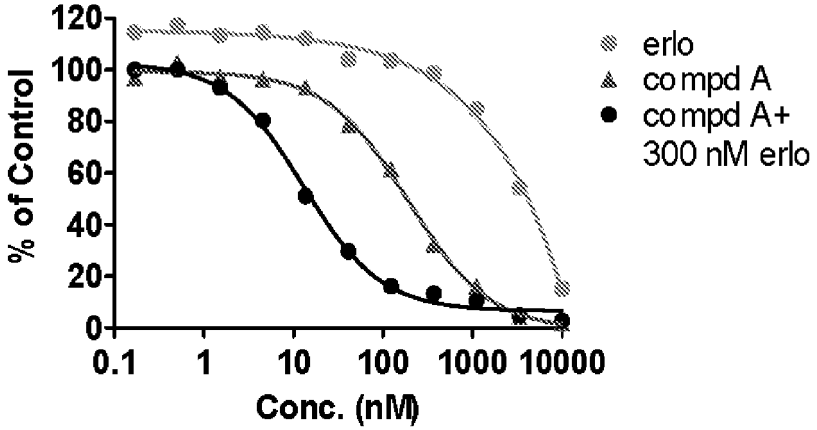
IC_{50} RPC9 clone 6=1974 nM

Figure 3

A


120
100
80
60
40
20
0
% of Control
0.1
1
10
100
1000
10000
Conc. (nM)
daco
compd A
compd A+4 nM daco

B


120
100
80
60
40
20
0
% of Control
0.1
1
10
100
1000
10000
Conc. (nM)
erlo
compd A
compd A+
300 nM erlo

C

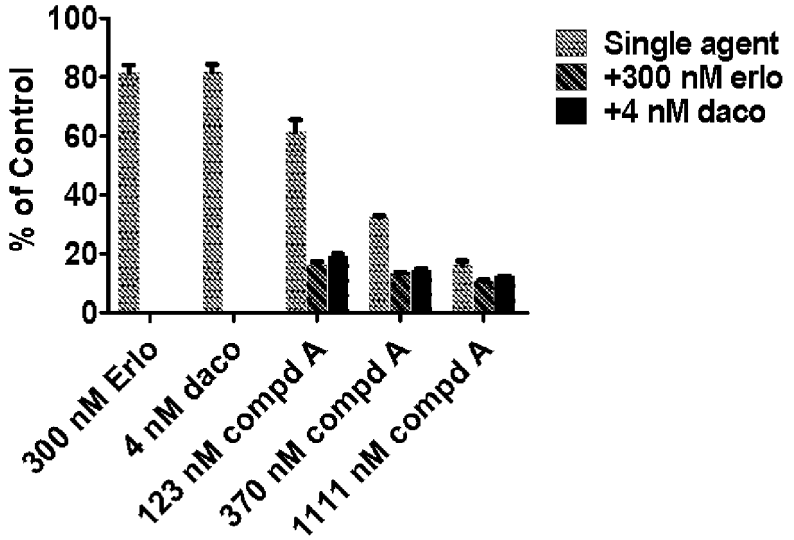
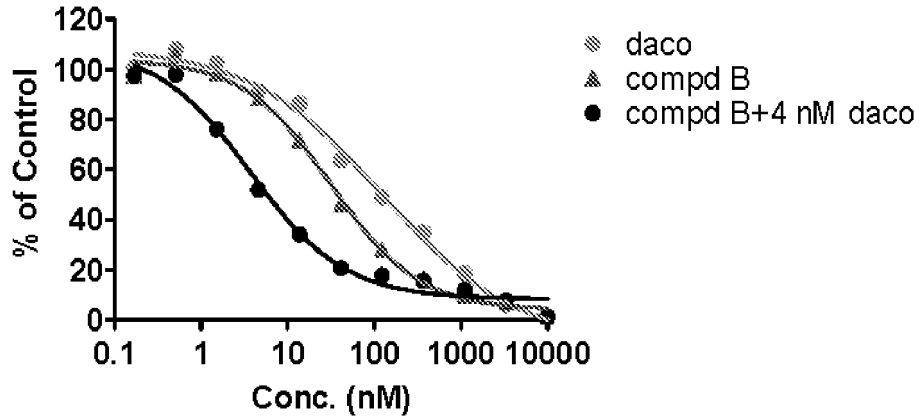
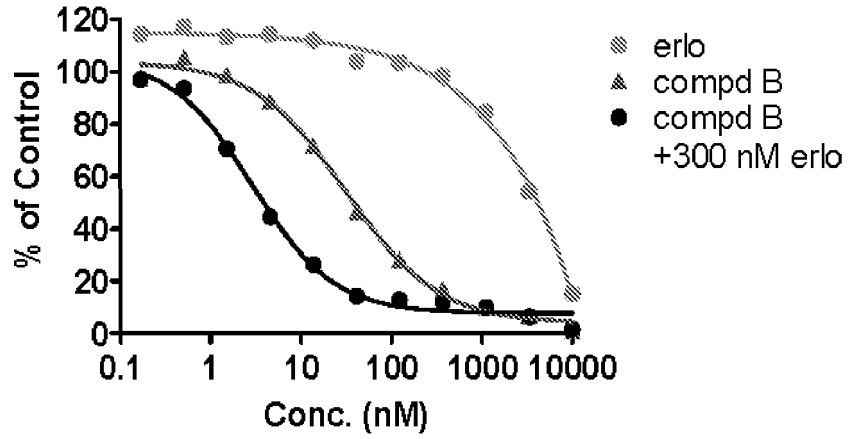

100
80
60
40
20
0
% of Control
Single agent
+300 nM erlo
+4 nM daco
300 nM Erlo
4 nM daco
123 nM compd A
370 nM compd A
1111 nM compd A

Figure 4

A


120
100
80
60
40
20
0
% of Control
0.1
1
10
100
1000
10000
Conc. (nM)
daco
compd B
compd B+4 nM daco

B


120
100
80
60
40
20
0
% of Control
0.1
1
10
100
1000
10000
Conc. (nM)
erlo
compd B
compd B
+300 nM erlo

C

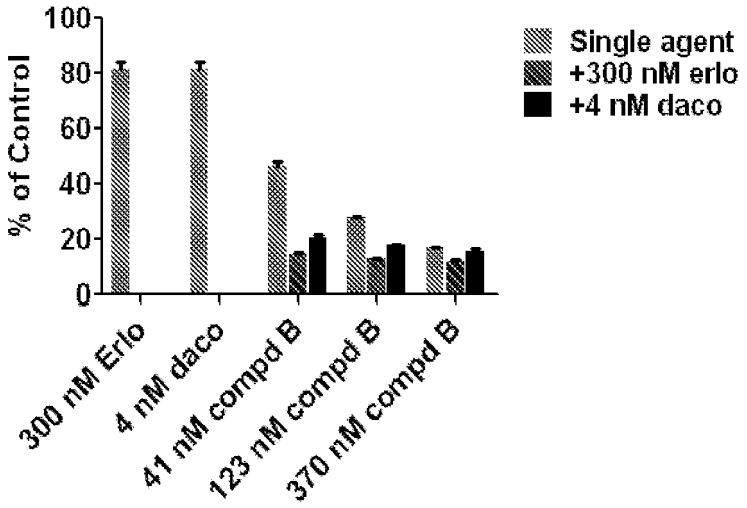

100
80
60
40
20
0
% of Control
Single agent
+300 nM erlo
+4 nM daco
300 nM Erlo
4 nM daco
41 nM compd B
123 nM compd B
370 nM compd B

Figure 5

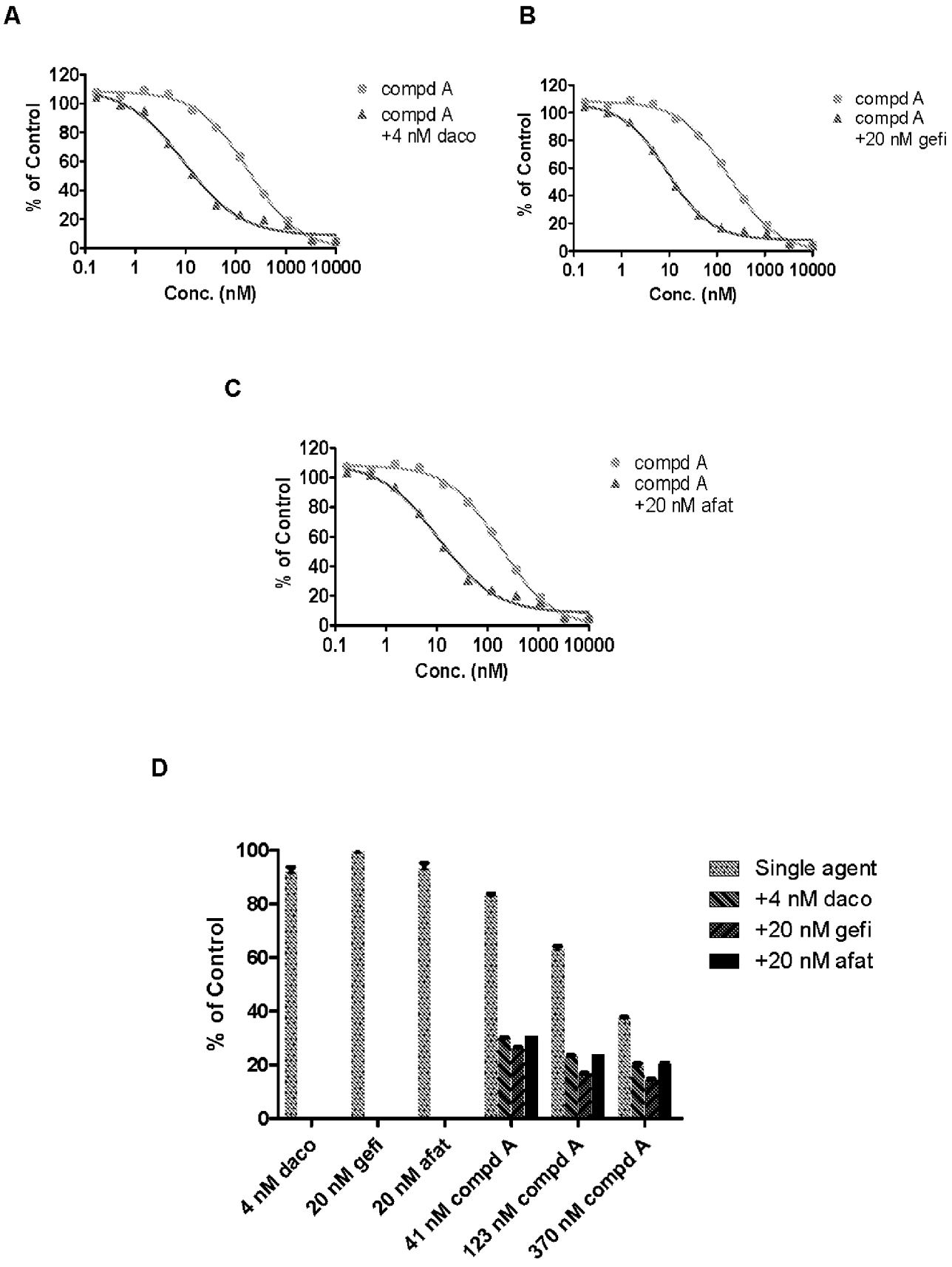

A
% of Control
120
100
80
60
40
20
0
0.1
1
10
100
1000
10000
Conc. (nM)
compd A
compd A
+4 nM daco
B
% of Control
Conc. (nM)
compd A
compd A
+20 nM gefi
C
% of Control
Conc. (nM)
compd A
compd A
+20 nM afat
D
% of Control
100
80
60
40
20
0
4 nM daco
20 nM gefi
20 nM afat
41 nM compd A
123 nM compd A
370 nM compd A
Single agent
+4 nM daco
+20 nM gefi
+20 nM afat

Figure 6

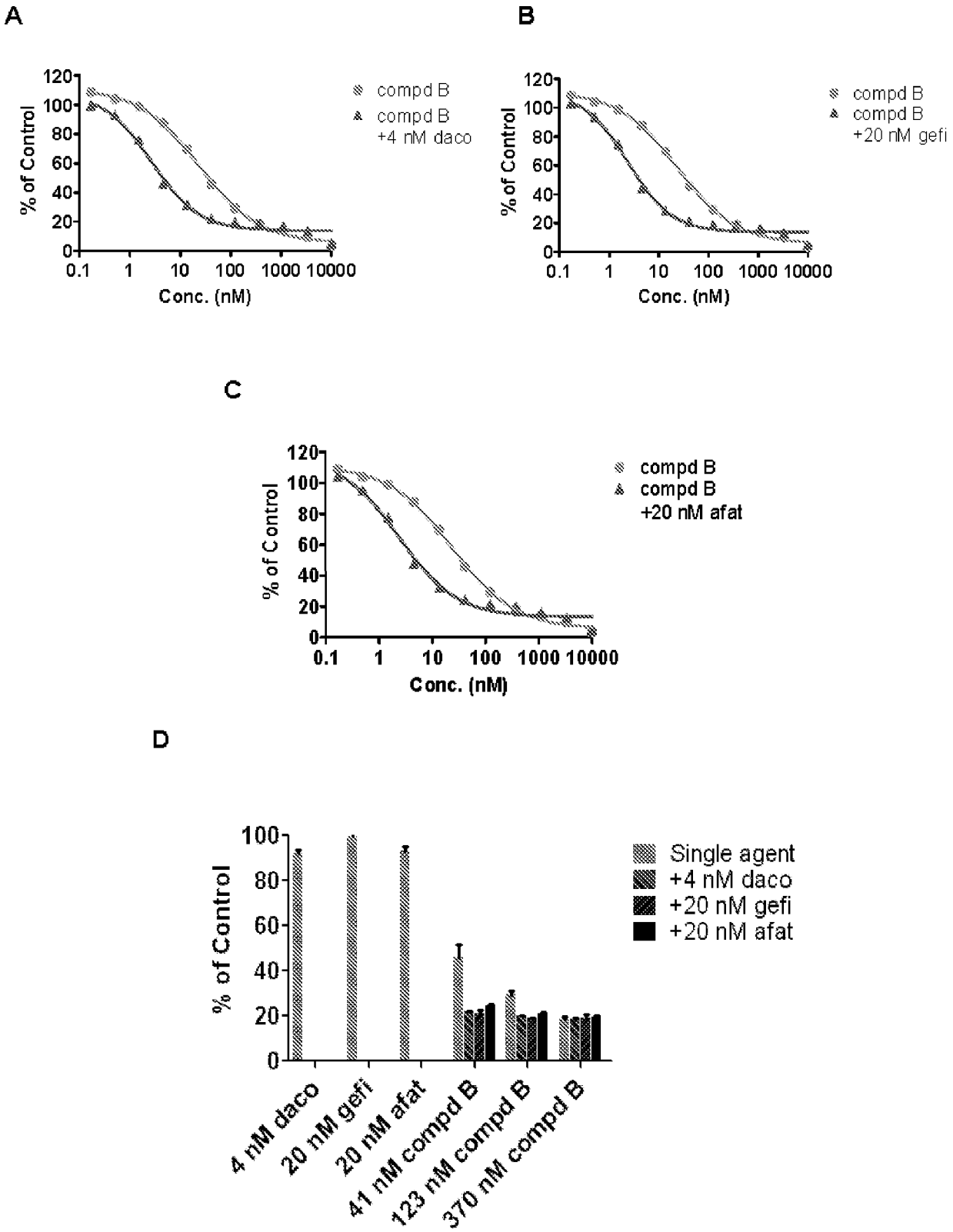
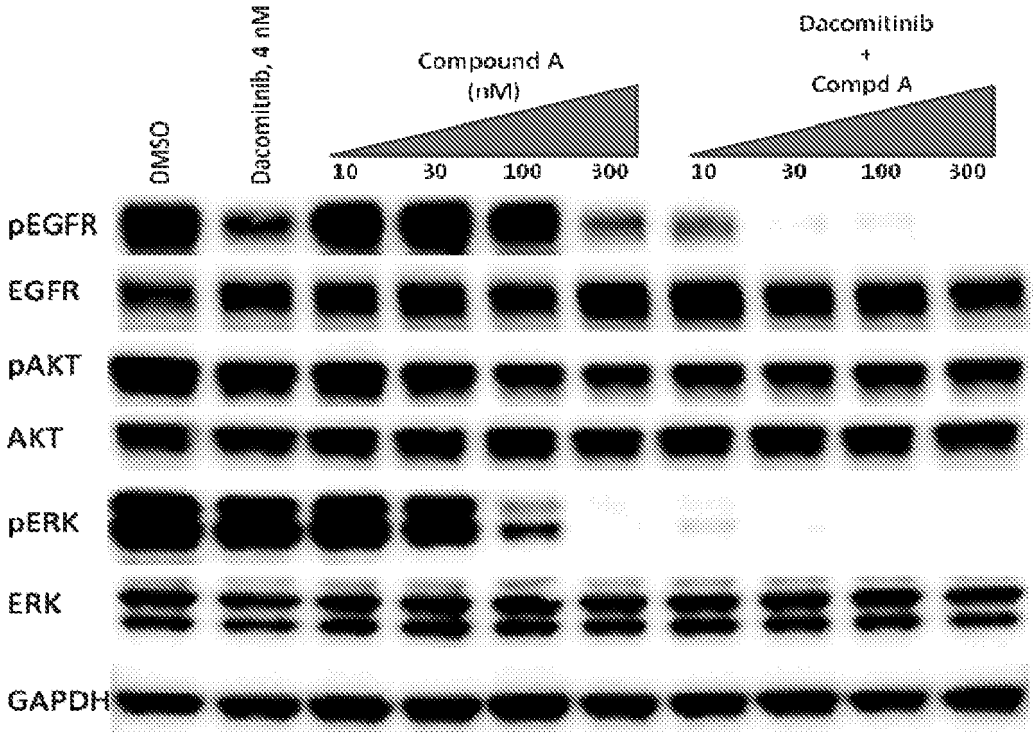

A
% of Control
120
100
80
60
40
20
0
0.1
1
10
100
1000
10000
Conc. (nM)
compd B
compd B
+4 nM daco
B
% of Control
Conc. (nM)
compd B
compd B
+20 nM gefi
C
% of Control
Conc. (nM)
compd B
compd B
+20 nM afat
D
% of Control
100
80
60
40
20
0
4 nM daco
20 nM gefi
20 nM afat
41 nM compd B
123 nM compd B
370 nM compd B
Single agent
+4 nM daco
+20 nM gefi
+20 nM afat

Figure 7

A


DMSO
Dacomitinib, 4 nM
Compound A (nM)
10
30
100
300
Dacomitinib + Compd A
10
30
100
300
pEGFR
EGFR
pAKT
AKT
pERK
ERK
GAPDH

B

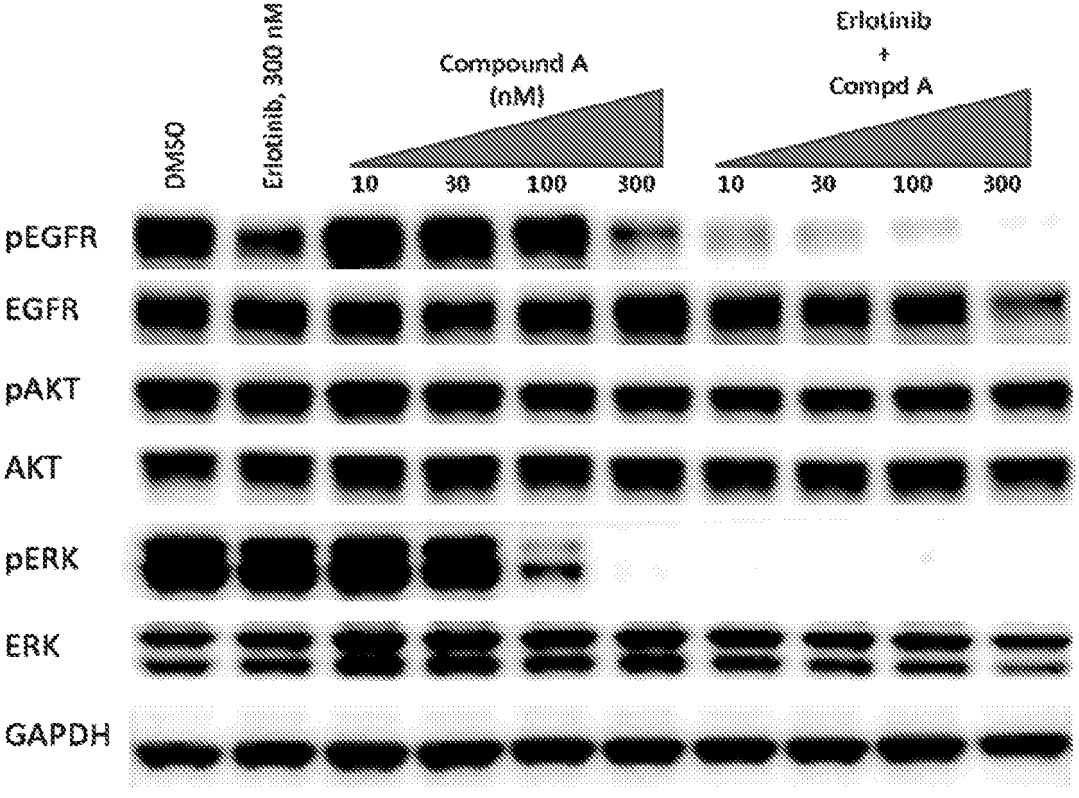

DMSO
Erlotinib, 300 nM
Compound A (nM)
10
30
100
300
Erlotinib + Compd A
10
30
100
300
pEGFR
EGFR
pAKT
AKT
pERK
ERK
GAPDH

Figure 8

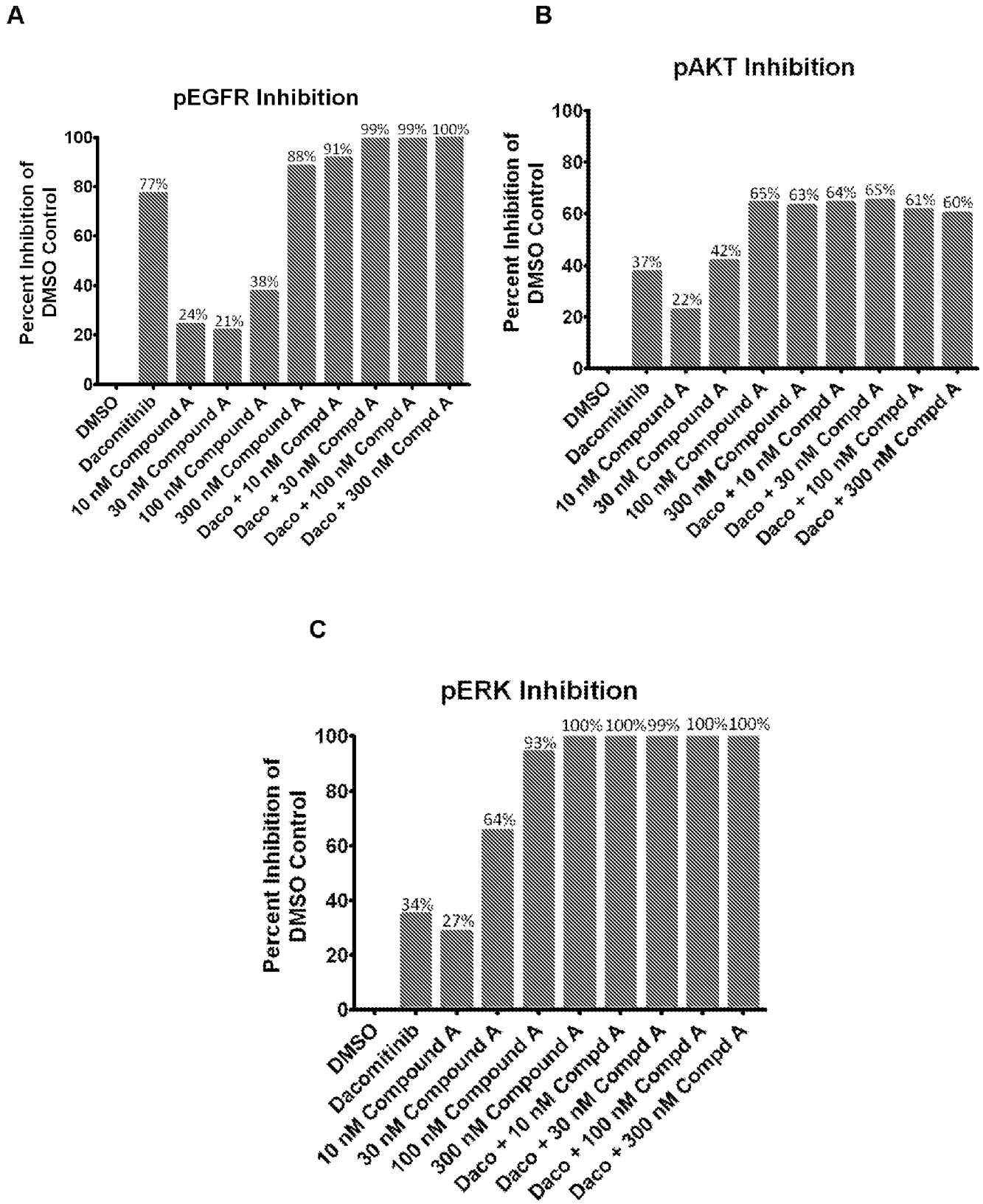

A
pEGFR Inhibition
Percent Inhibition of DMSO Control
100
80
60
40
20
0
77%
24%
21%
38%
88%
91%
99%
99%
100%
DMSO
Dacomitinib
10 nM Compound A
30 nM Compound A
100 nM Compound A
300 nM Compound A
Daco + 10 nM Compd A
Daco + 30 nM Compd A
Daco + 100 nM Compd A
Daco + 300 nM Compd A
B
pAKT Inhibition
Percent Inhibition of DMSO Control
100
80
60
40
20
0
37%
22%
42%
65%
63%
64%
65%
61%
60%
DMSO
Dacomitinib
10 nM Compound A
30 nM Compound A
100 nM Compound A
300 nM Compound A
Daco + 10 nM Compd A
Daco + 30 nM Compd A
Daco + 100 nM Compd A
Daco + 300 nM Compd A
C
pERK Inhibition
Percent Inhibition of DMSO Control
100
80
60
40
20
0
34%
27%
64%
93%
100%
100%
99%
100%
100%
DMSO
Dacomitinib
10 nM Compound A
30 nM Compound A
100 nM Compound A
300 nM Compound A
Daco + 10 nM Compd A
Daco + 30 nM Compd A
Daco + 100 nM Compd A
Daco + 300 nM Compd A

Figure 9

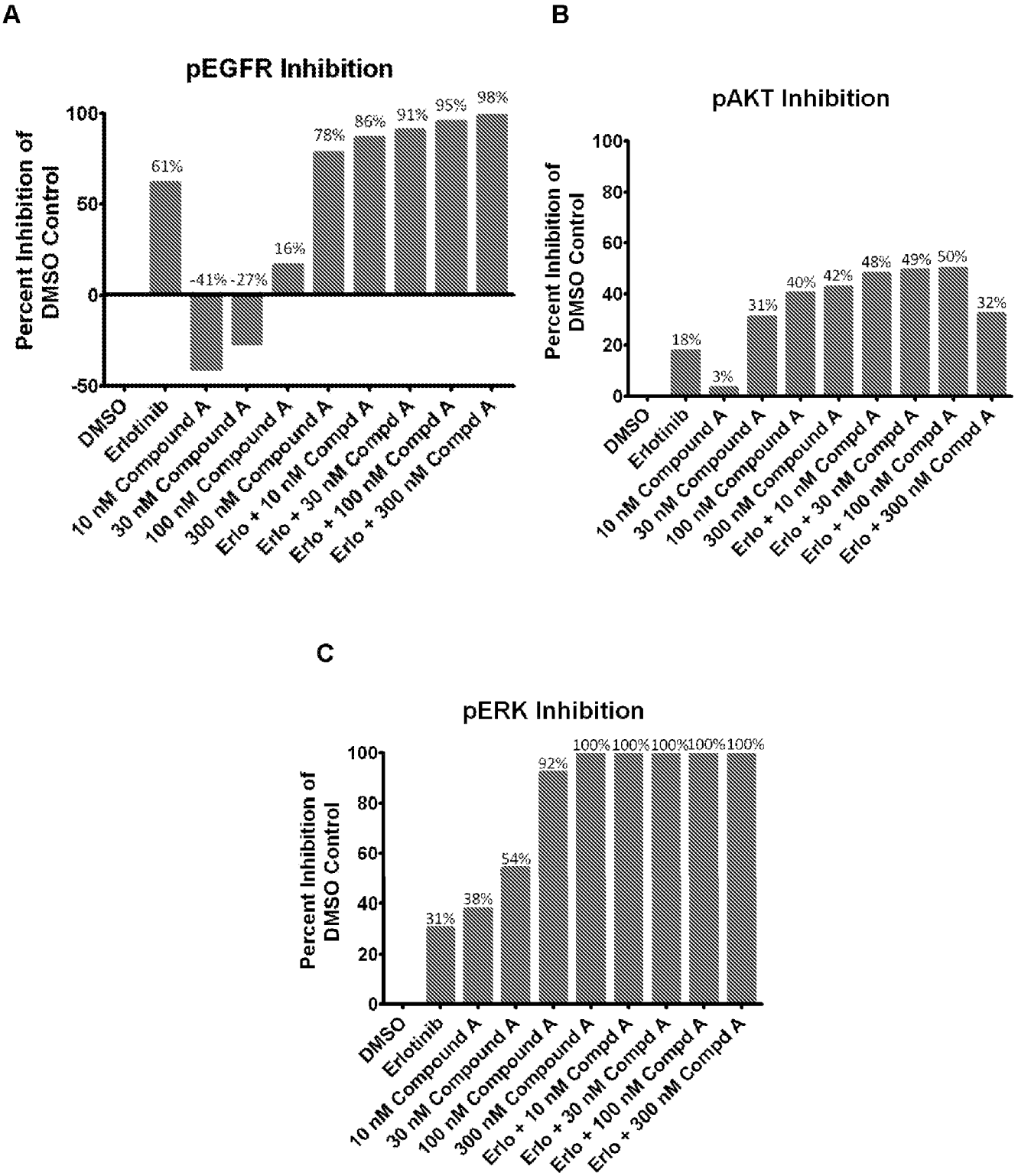
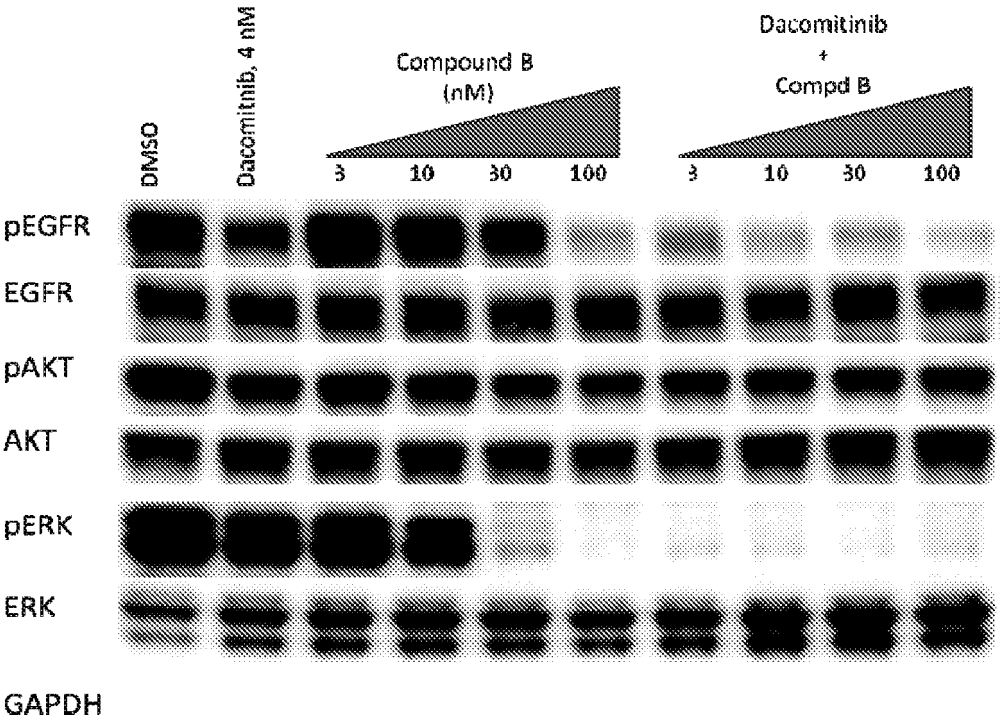

A
pEGFR Inhibition
Percent Inhibition of DMSO Control
100
50
0
-50
61%
-41%
-27%
16%
78%
86%
91%
95%
98%
DMSO
Erlotinib
10 nM Compound A
30 nM Compound A
100 nM Compound A
300 nM Compound A
Erlo + 10 nM Compd A
Erlo + 30 nM Compd A
Erlo + 100 nM Compd A
Erlo + 300 nM Compd A
B
pAKT Inhibition
Percent Inhibition of DMSO Control
100
80
60
40
20
0
18%
3%
31%
40%
42%
48%
49%
50%
32%
DMSO
Erlotinib
10 nM Compound A
30 nM Compound A
100 nM Compound A
300 nM Compound A
Erlo + 10 nM Compd A
Erlo + 30 nM Compd A
Erlo + 100 nM Compd A
Erlo + 300 nM Compd A
C
pERK Inhibition
Percent Inhibition of DMSO Control
100
80
60
40
20
0
31%
38%
54%
92%
100%
100%
100%
100%
100%
DMSO
Erlotinib
10 nM Compound A
30 nM Compound A
100 nM Compound A
300 nM Compound A
Erlo + 10 nM Compd A
Erlo + 30 nM Compd A
Erlo + 100 nM Compd A
Erlo + 300 nM Compd A

Figure 10

A


DMSO
Dacomitinib, 4 nM
Compound B (nM)
3
10
30
100
Dacomitinib + Compd B
3
10
30
100
pEGFR
EGFR
pAKT
AKT
pERK
ERK
GAPDH

B

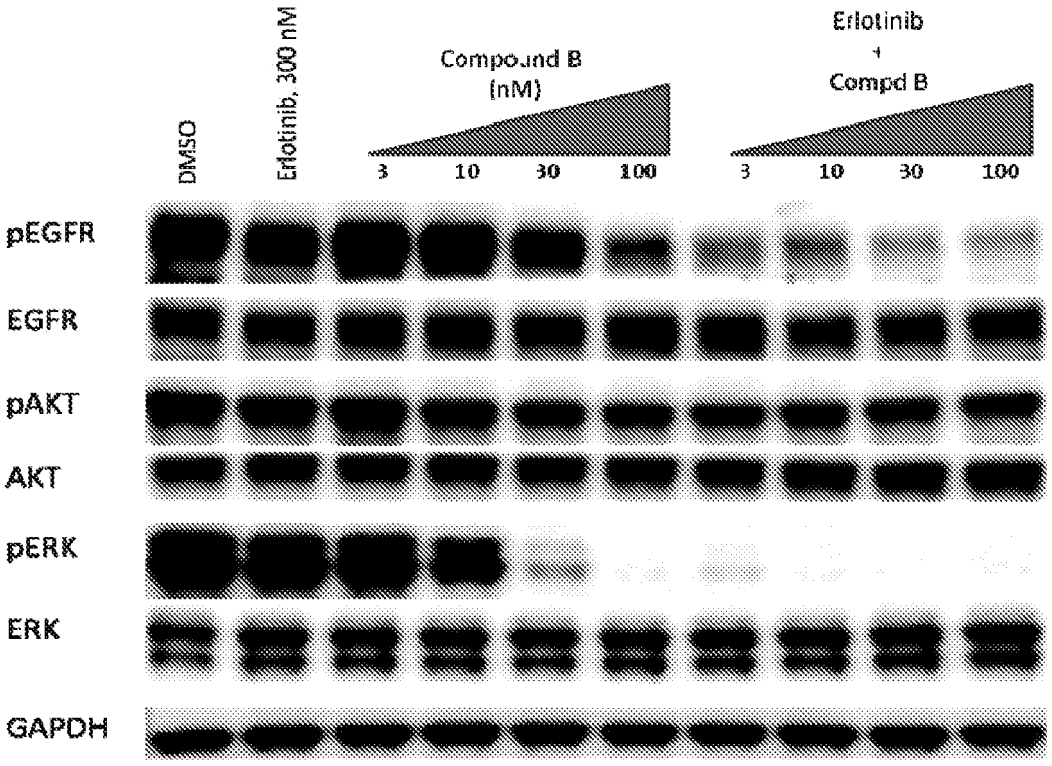

DMSO
Erlotinib, 300 nM
Compound B (nM)
3
10
30
100
Erlotinib + Compd B
3
10
30
100
pEGFR
EGFR
pAKT
AKT
pERK
ERK
GAPDH

Figure 11

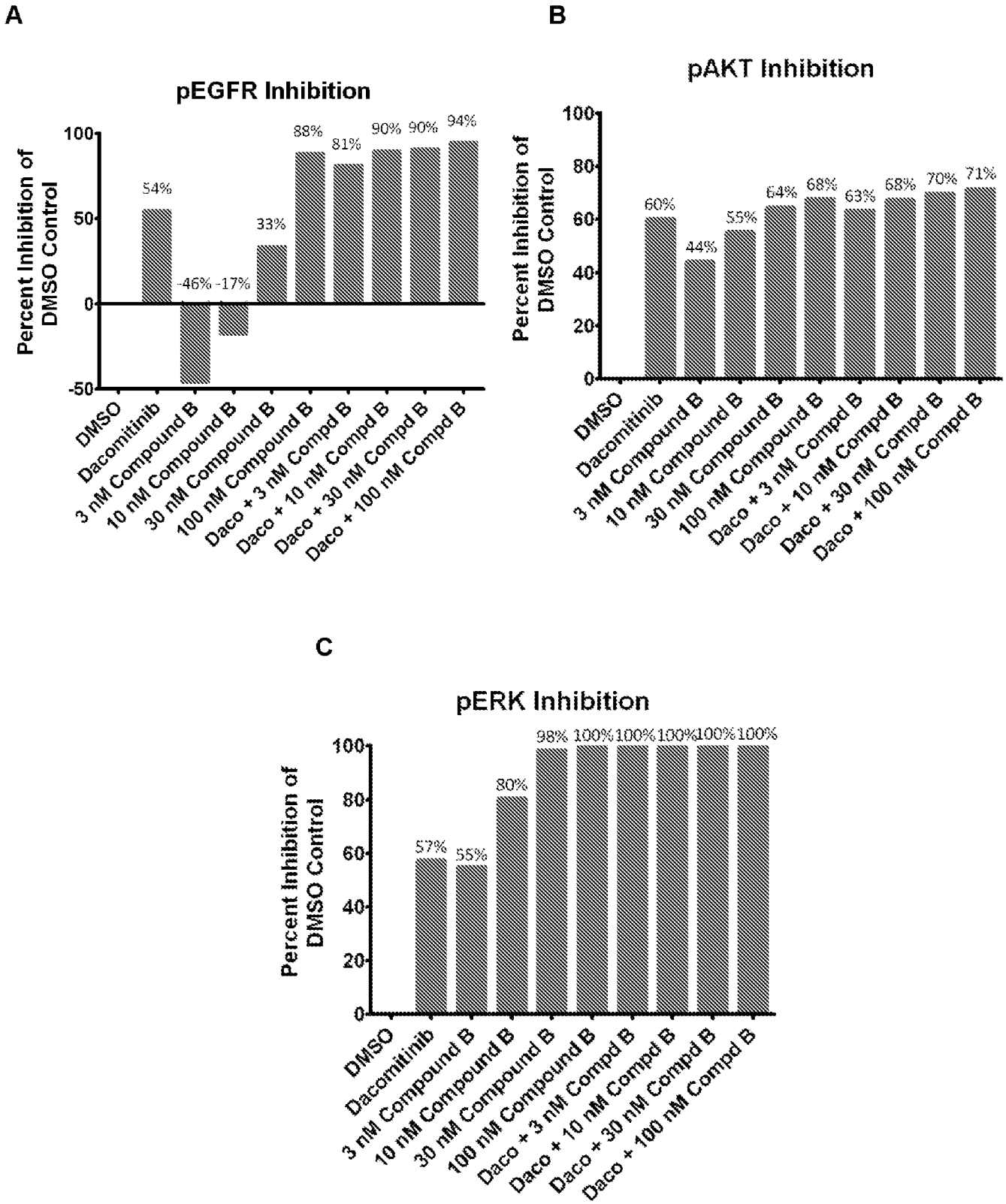

A
pEGFR Inhibition
Percent Inhibition of DMSO Control
100
50
0
-50
54%
-46%
-17%
33%
88%
81%
90%
90%
94%
DMSO
Dacomitinib
3 nM Compound B
10 nM Compound B
30 nM Compound B
100 nM Compound B
Daco + 3 nM Compd B
Daco + 10 nM Compd B
Daco + 30 nM Compd B
Daco + 100 nM Compd B
B
pAKT Inhibition
Percent Inhibition of DMSO Control
100
80
60
40
20
0
60%
44%
55%
64%
68%
63%
68%
70%
71%
DMSO
Dacomitinib
3 nM Compound B
10 nM Compound B
30 nM Compound B
100 nM Compound B
Daco + 3 nM Compd B
Daco + 10 nM Compd B
Daco + 30 nM Compd B
Daco + 100 nM Compd B
C
pERK Inhibition
Percent Inhibition of DMSO Control
100
80
60
40
20
0
57%
55%
80%
98%
100%
100%
100%
100%
100%
DMSO
Dacomitinib
3 nM Compound B
10 nM Compound B
30 nM Compound B
100 nM Compound B
Daco + 3 nM Compd B
Daco + 10 nM Compd B
Daco + 30 nM Compd B
Daco + 100 nM Compd B

Figure 12

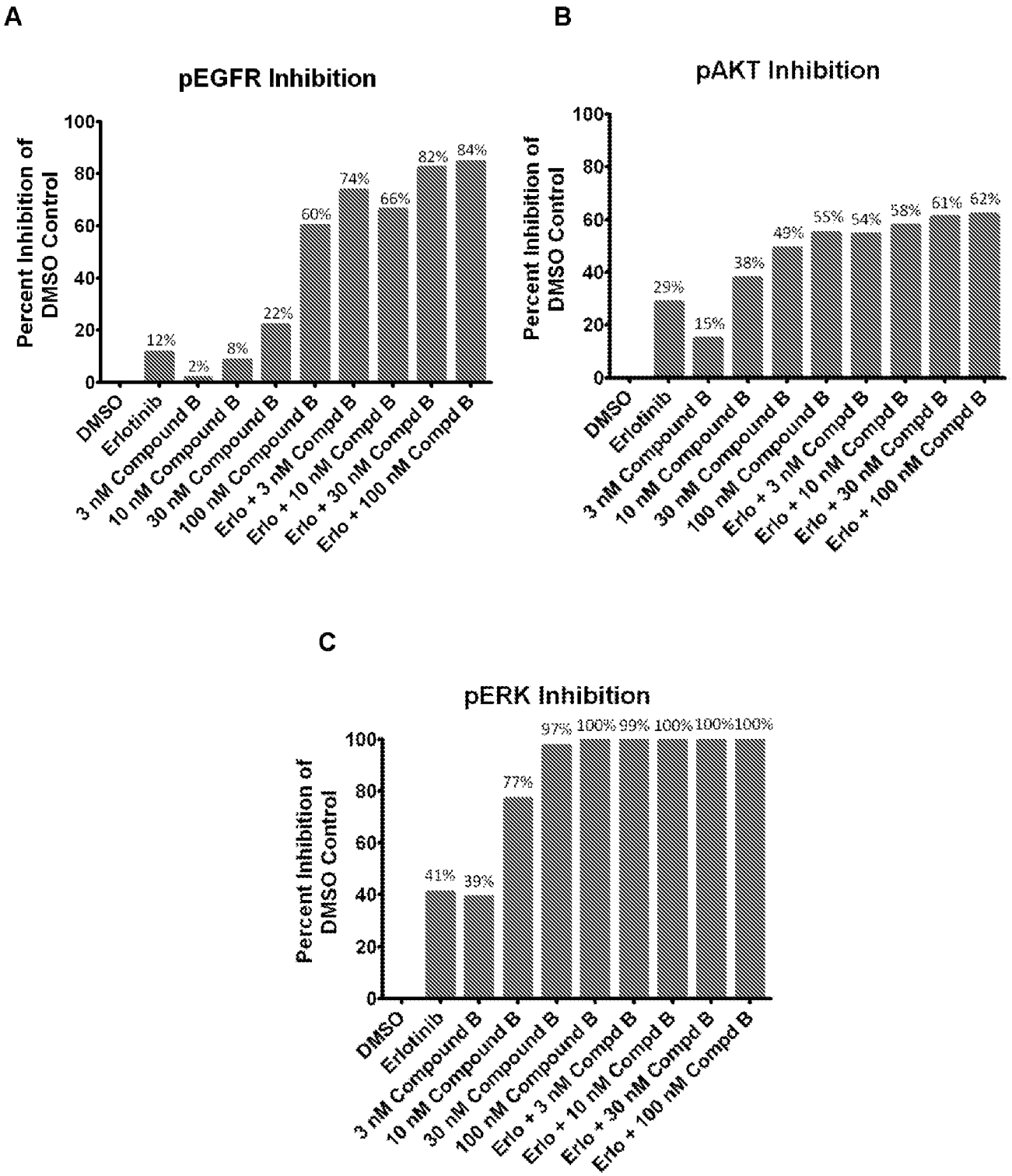
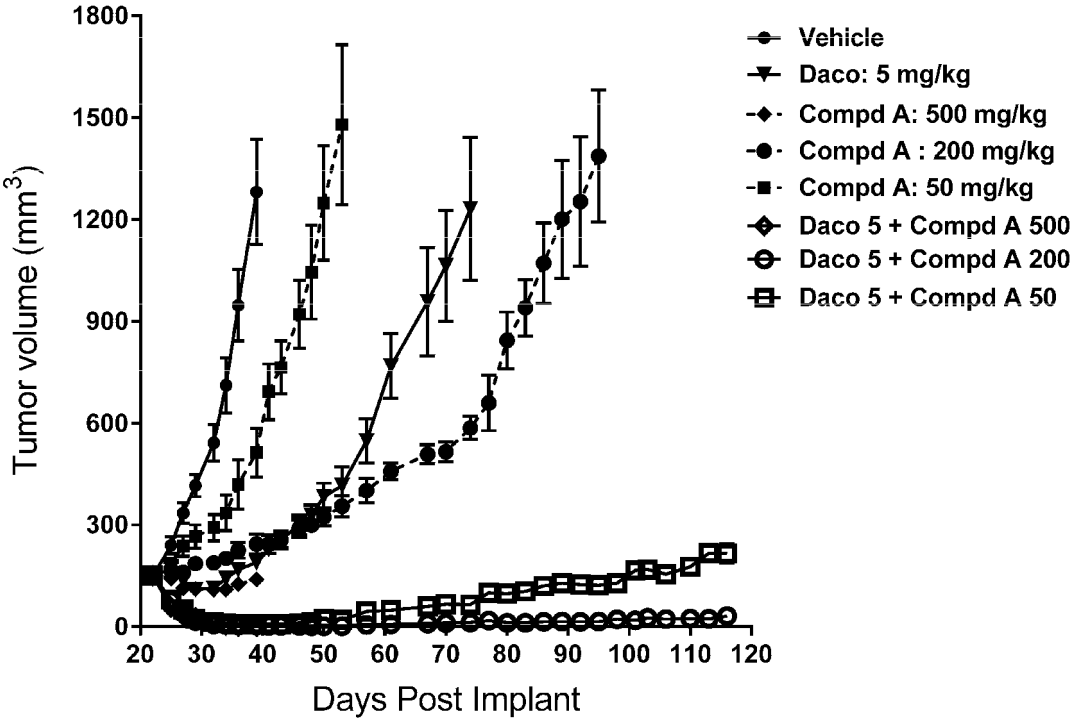

A
pEGFR Inhibition
Percent Inhibition of DMSO Control
100
80
60
40
20
0
12%
2%
8%
22%
60%
74%
66%
82%
84%
DMSO
Erlotinib
3 nM Compound B
10 nM Compound B
30 nM Compound B
100 nM Compound B
Erlo + 3 nM Compd B
Erlo + 10 nM Compd B
Erlo + 30 nM Compd B
Erlo + 100 nM Compd B
B
pAKT Inhibition
Percent Inhibition of DMSO Control
100
80
60
40
20
0
29%
15%
38%
49%
55%
54%
58%
61%
62%
DMSO
Erlotinib
3 nM Compound B
10 nM Compound B
30 nM Compound B
100 nM Compound B
Erlo + 3 nM Compd B
Erlo + 10 nM Compd B
Erlo + 30 nM Compd B
Erlo + 100 nM Compd B
C
pERK Inhibition
Percent Inhibition of DMSO Control
100
80
60
40
20
0
41%
39%
77%
97%
100%
99%
100%
100%
100%
DMSO
Erlotinib
3 nM Compound B
10 nM Compound B
30 nM Compound B
100 nM Compound B
Erlo + 3 nM Compd B
Erlo + 10 nM Compd B
Erlo + 30 nM Compd B
Erlo + 100 nM Compd B

Figure 13

A


Tumor volume (mm3)
1800
1500
1200
900
600
300
0
20 30 40 50 60 70 80 90 100 110 120
Days Post Implant
Vehicle
Daco: 5 mg/kg
Compd A: 500 mg/kg
Compd A : 200 mg/kg
Compd A: 50 mg/kg
Daco 5 + Compd A 500
Daco 5 + Compd A 200
Daco 5 + Compd A 50

B

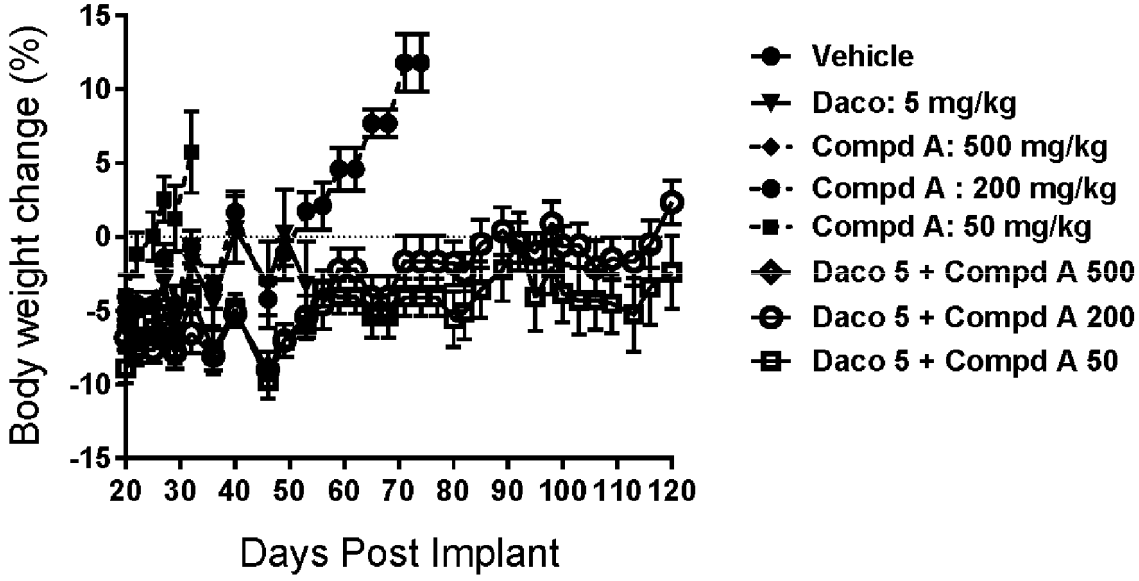
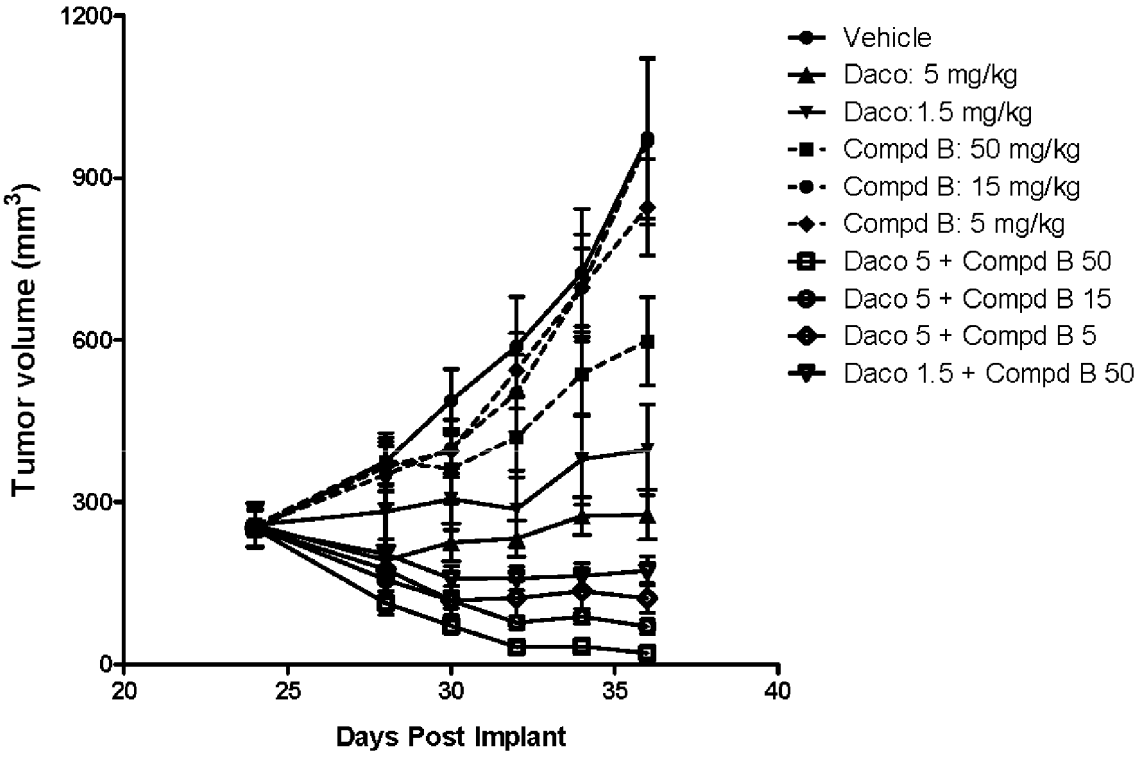

Body weight change (%)
15
10
5
0
-5
-10
-15
20 30 40 50 60 70 80 90 100 110 120
Days Post Implant
Vehicle
Daco: 5 mg/kg
Compd A: 500 mg/kg
Compd A : 200 mg/kg
Compd A: 50 mg/kg
Daco 5 + Compd A 500
Daco 5 + Compd A 200
Daco 5 + Compd A 50

Figure 14

A


1200
900
600
300
0
Tumor volume (mm3)
20
25
30
35
40
Days Post Implant
Vehicle
Daco: 5 mg/kg
Daco:1.5 mg/kg
Compd B: 50 mg/kg
Compd B: 15 mg/kg
Compd B: 5 mg/kg
Daco 5 + Compd B 50
Daco 5 + Compd B 15
Daco 5 + Compd B 5
Daco 1.5 + Compd B 50

B

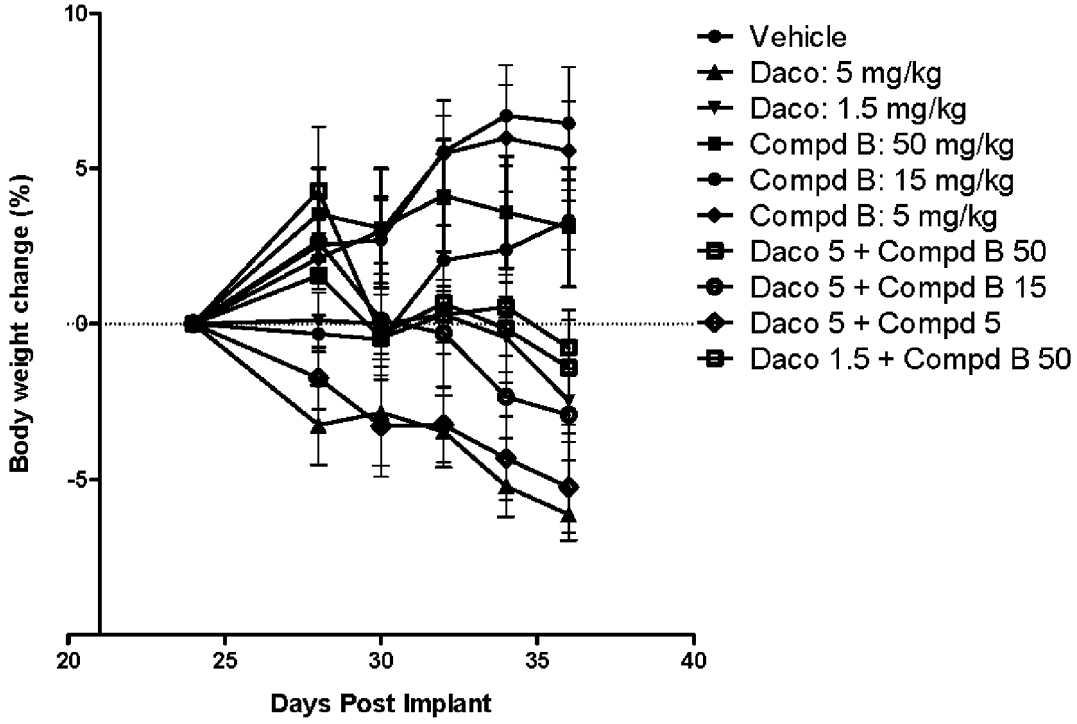
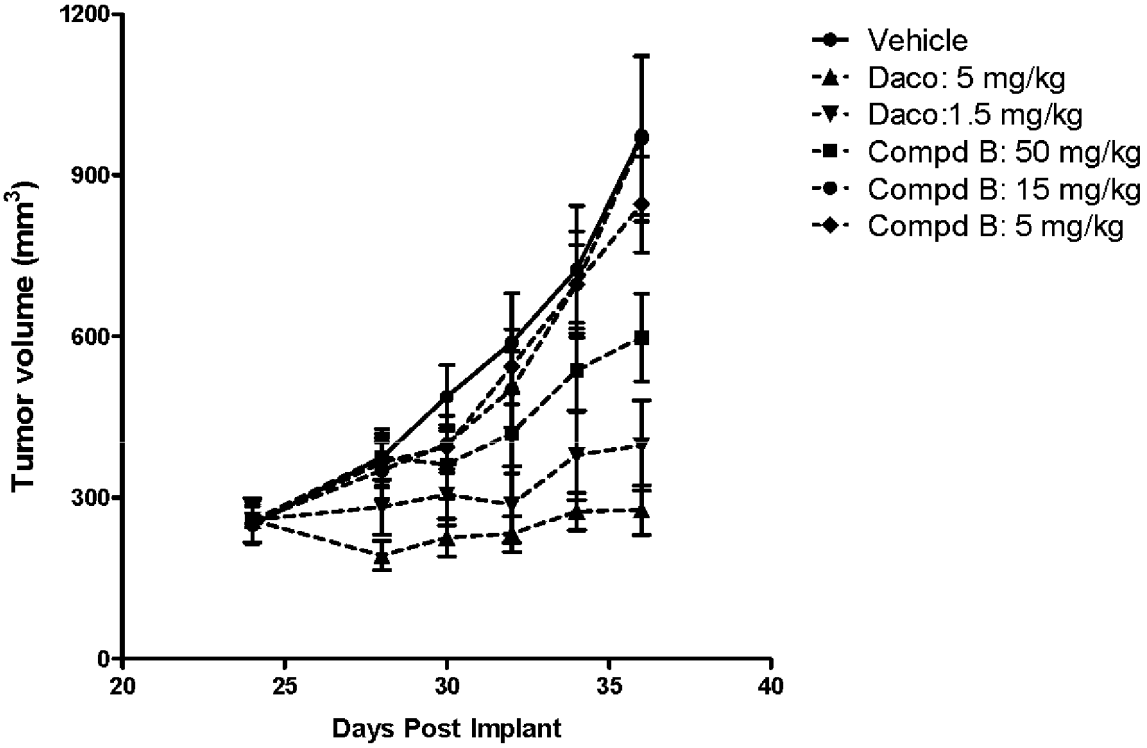

10
5
0
-5
Body weight change (%)
20
25
30
35
40
Days Post Implant
Vehicle
Daco: 5 mg/kg
Daco: 1.5 mg/kg
Compd B: 50 mg/kg
Compd B: 15 mg/kg
Compd B: 5 mg/kg
Daco 5 + Compd B 50
Daco 5 + Compd B 15
Daco 5 + Compd 5
Daco 1.5 + Compd B 50

Figure 15

A


1200
900
600
300
0
Tumor volume (mm3)
20
25
30
35
40
Days Post Implant
Vehicle
Daco: 5 mg/kg
Daco:1.5 mg/kg
Compd B: 50 mg/kg
Compd B: 15 mg/kg
Compd B: 5 mg/kg

B

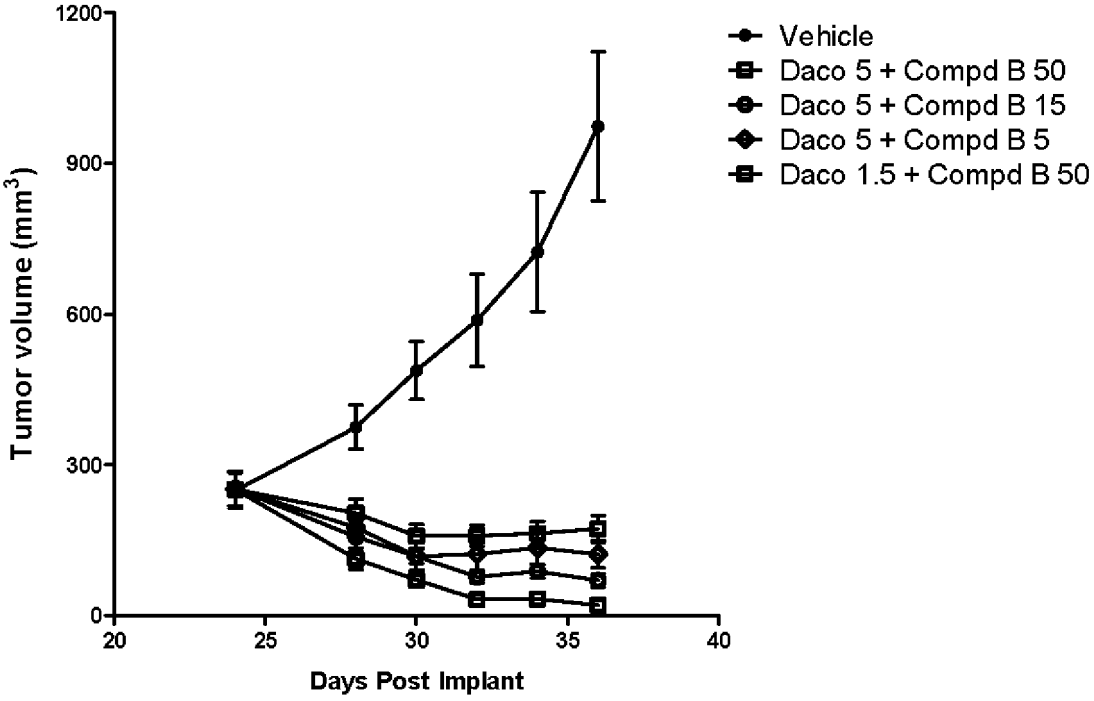
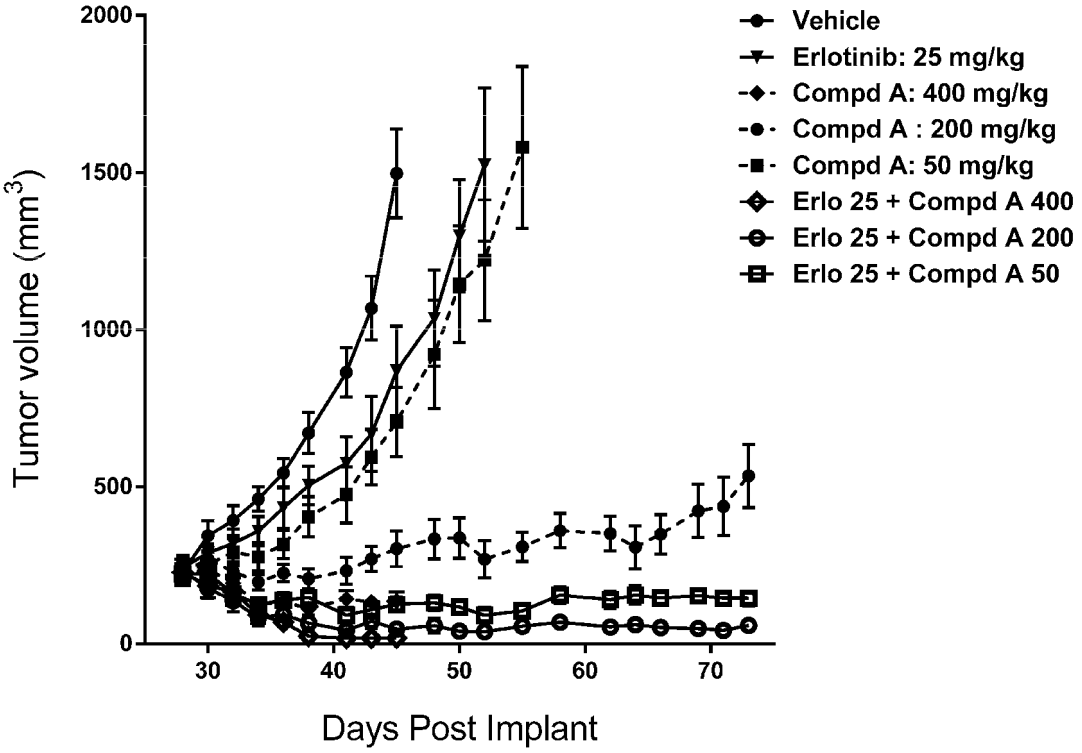
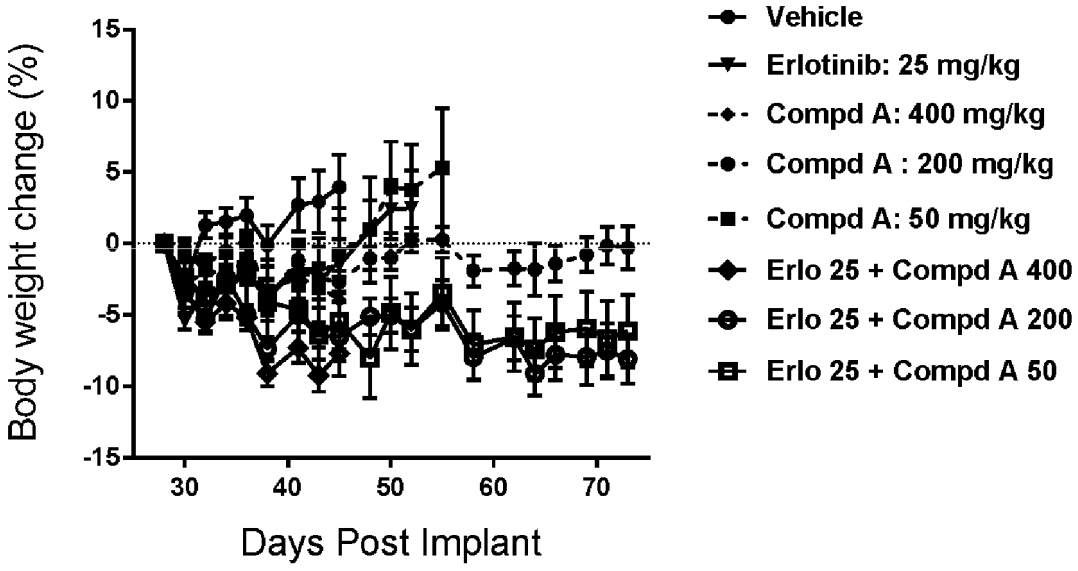

1200
900
600
300
0
Tumor volume (mm3)
20
25
30
35
40
Days Post Implant
Vehicle
Daco 5 + Compd B 50
Daco 5 + Compd B 15
Daco 5 + Compd B 5
Daco 1.5 + Compd B 50

Figure 16

A


Tumor volume (mm3)
2000
1500
1000
500
0
30
40
50
60
70
Days Post Implant
Vehicle
Erlotinib: 25 mg/kg
Compd A: 400 mg/kg
Compd A : 200 mg/kg
Compd A: 50 mg/kg
Erlo 25 + Compd A 400
Erlo 25 + Compd A 200
Erlo 25 + Compd A 50

B


Body weight change (%)
15
10
5
0
-5
-10
-15
30
40
50
60
70
Days Post Implant
Vehicle
Erlotinib: 25 mg/kg
Compd A: 400 mg/kg
Compd A : 200 mg/kg
Compd A: 50 mg/kg
Erlo 25 + Compd A 400
Erlo 25 + Compd A 200
Erlo 25 + Compd A 50