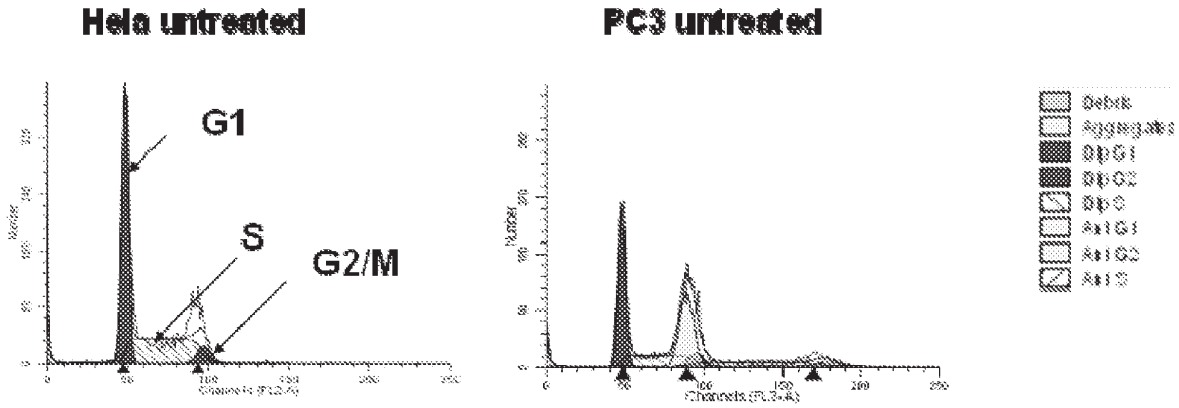


FIG. 1

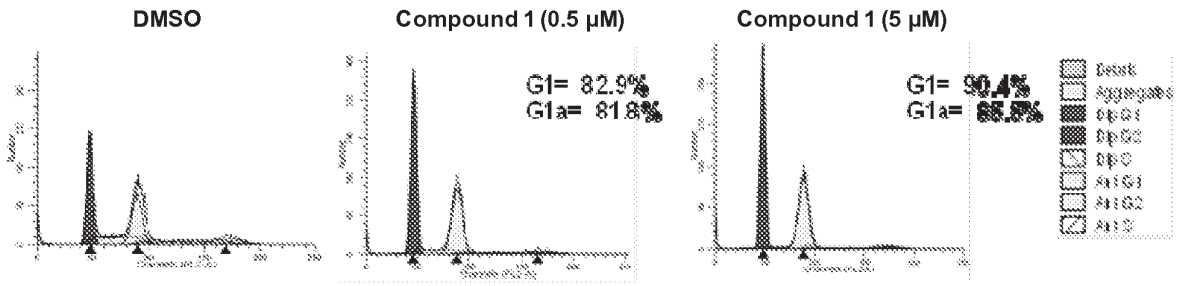

DMSO
Compound 1 (0.5 μM)
Compound 1 (5 μM)
G1= 82.9%
G1a= 81.8%
G1= 90.4%
G1a= 85.8%

FIG. 2

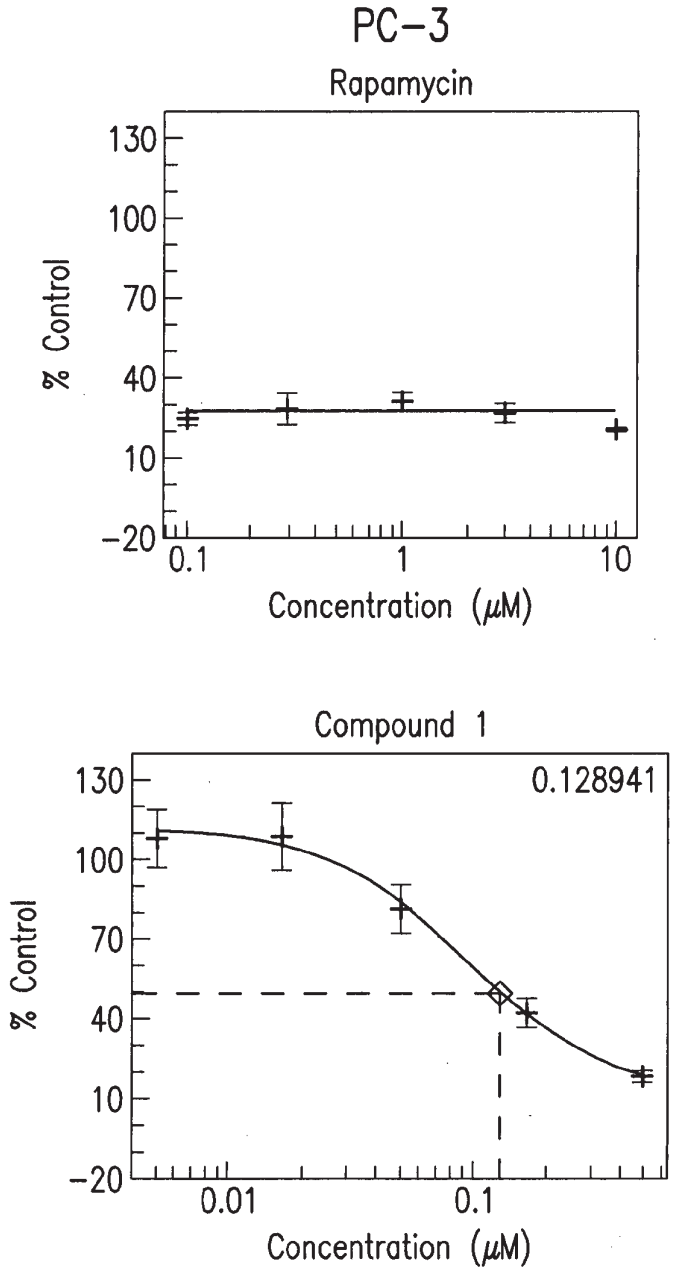

PC-3
Rapamycin
130
100
70
40
10
-20
% Control
0.1
1
10
Concentration (μM)
Compound 1
0.128941
130
100
70
40
10
-20
% Control
0.01
0.1
Concentration (μM)

FIG. 3

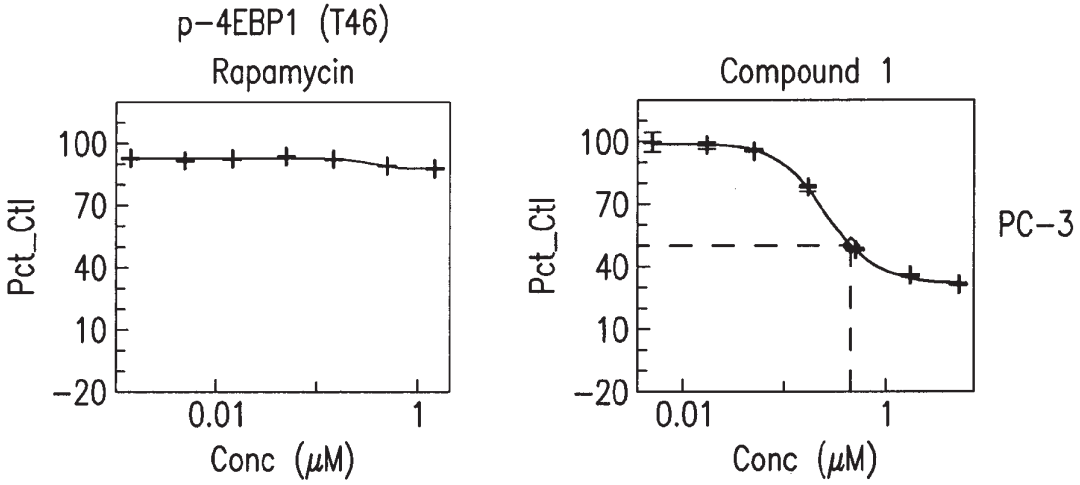

p-4EBP1 (T46)
Rapamycin
Compound 1
Pct_Ctl
100
70
40
10
-20
0.01
1
Conc (μM)
PC-3

FIG. 4

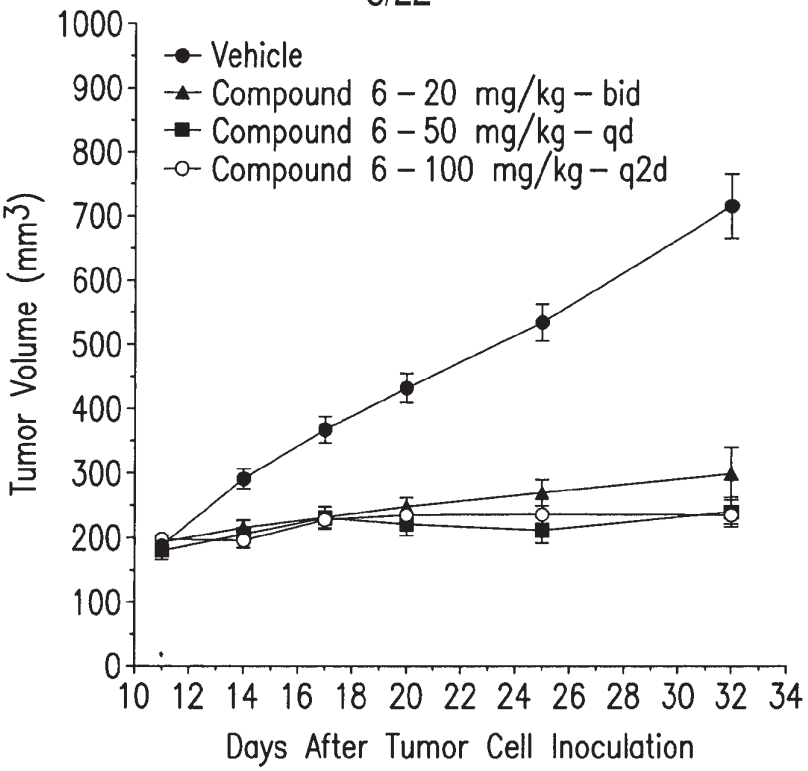

Vehicle
Compound 6 – 20 mg/kg – bid
Compound 6 – 50 mg/kg – qd
Compound 6 – 100 mg/kg – q2d
Tumor Volume (mm3)
1000
900
800
700
600
500
400
300
200
100
0
10 12 14 16 18 20 22 24 26 28 30 32 34
Days After Tumor Cell Inoculation

FIG. 5A

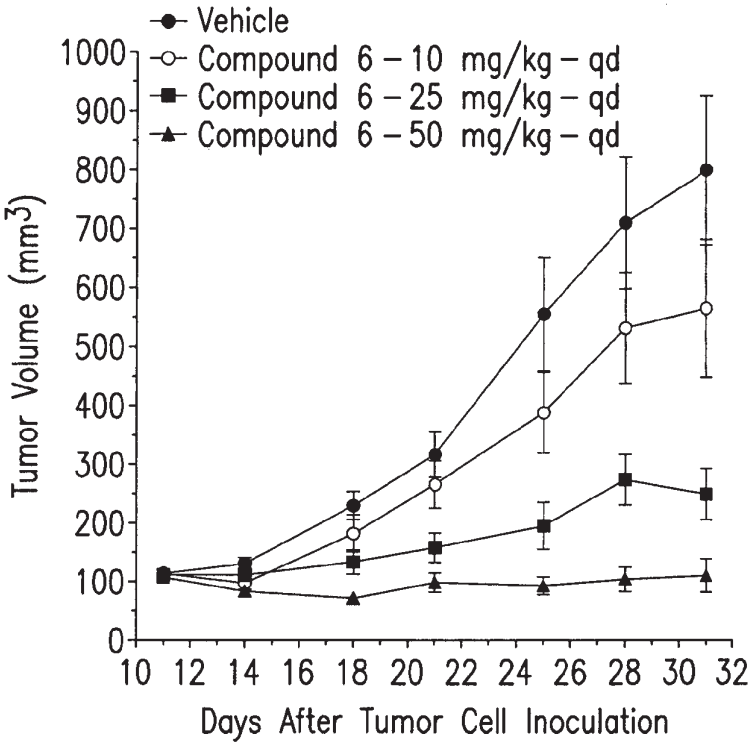

Vehicle
Compound 6 – 10 mg/kg – qd
Compound 6 – 25 mg/kg – qd
Compound 6 – 50 mg/kg – qd
Tumor Volume (mm3)
1000
900
800
700
600
500
400
300
200
100
0
10 12 14 16 18 20 22 24 26 28 30 32
Days After Tumor Cell Inoculation

FIG. 5B

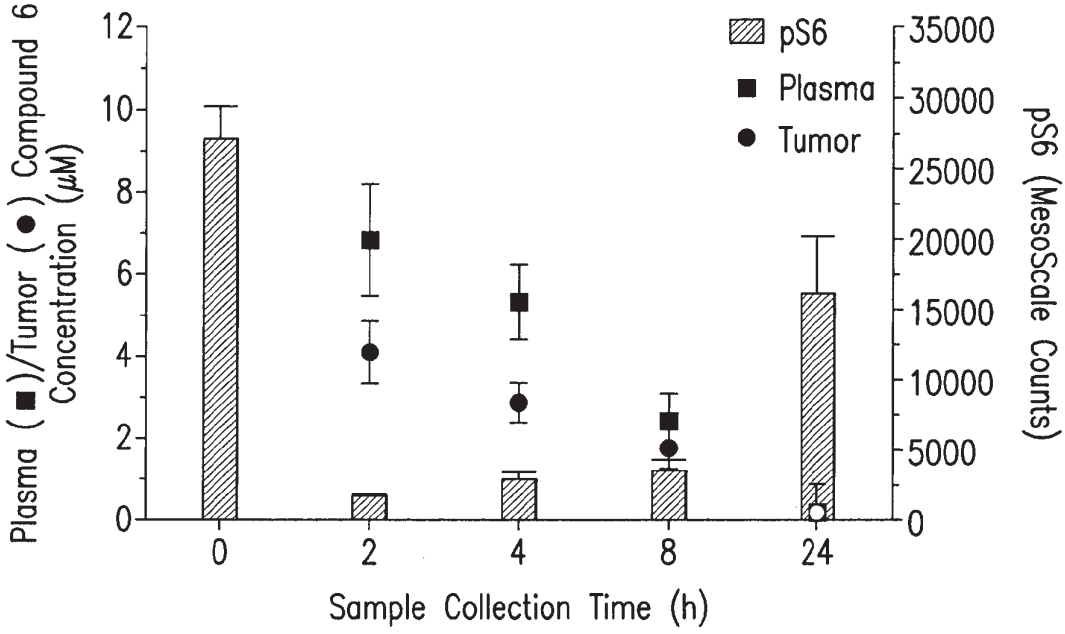

Plasma (■)/Tumor (●) Compound 6 Concentration (μM)
12
10
8
6
4
2
0
pS6
Plasma
Tumor
35000
30000
25000
20000
15000
10000
5000
0
pS6 (MesoScale Counts)
0
2
4
8
24
Sample Collection Time (h)

FIG. 6A

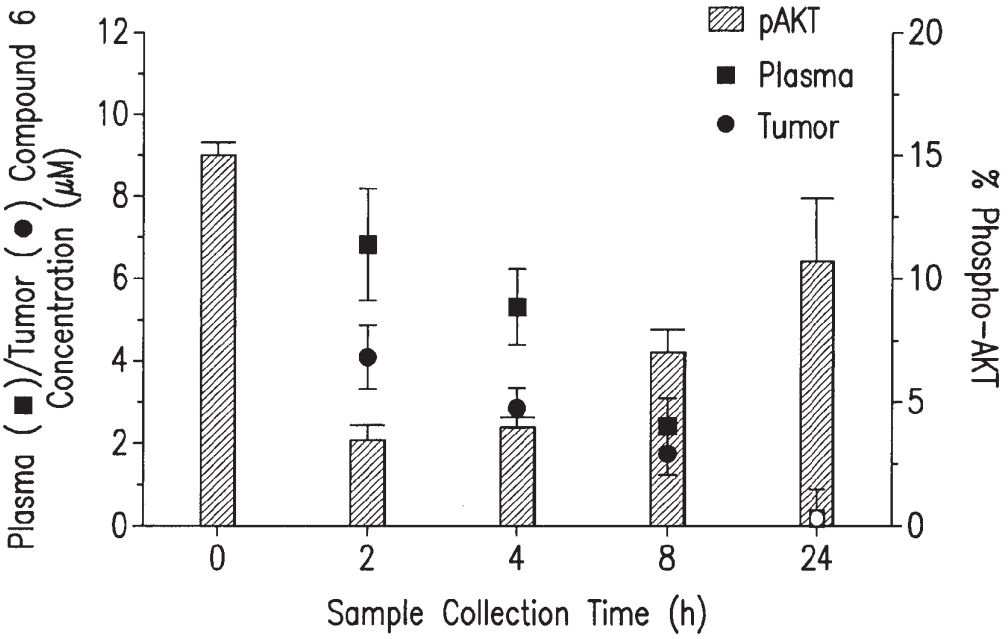

Plasma (■)/Tumor (●) Compound 6 Concentration (μM)
12
10
8
6
4
2
0
pAKT
Plasma
Tumor
20
15
10
5
0
% Phospho-AKT
0
2
4
8
24
Sample Collection Time (h)

FIG. 6B

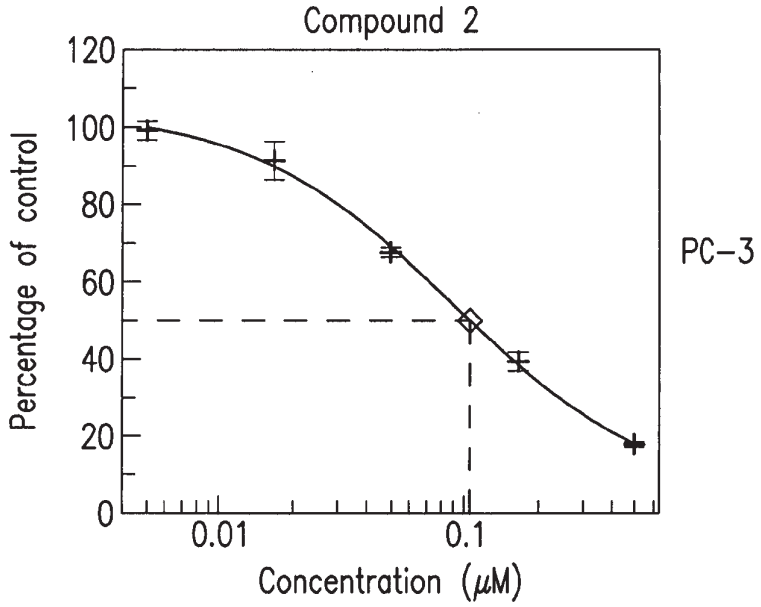

Compound 2
120
100
80
60
40
20
0
Percentage of control
0.01
0.1
Concentration (μM)
PC-3

FIG. 7

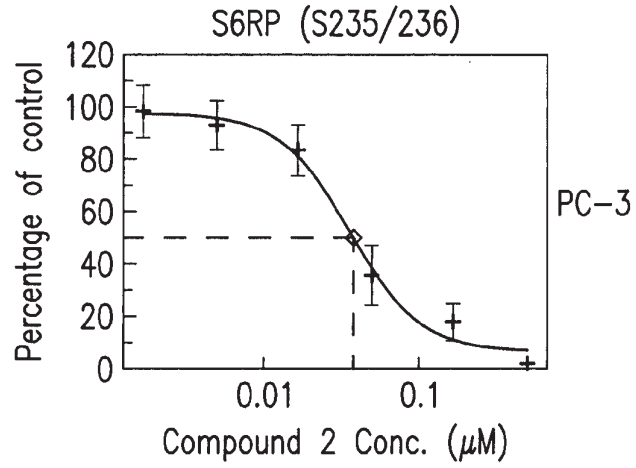


FIG. 8A

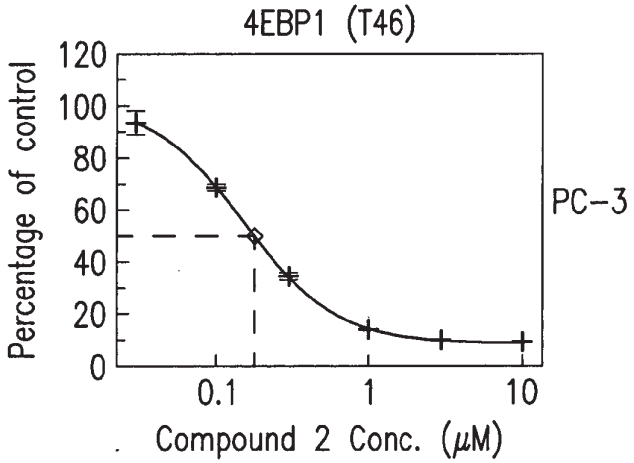


FIG. 8B

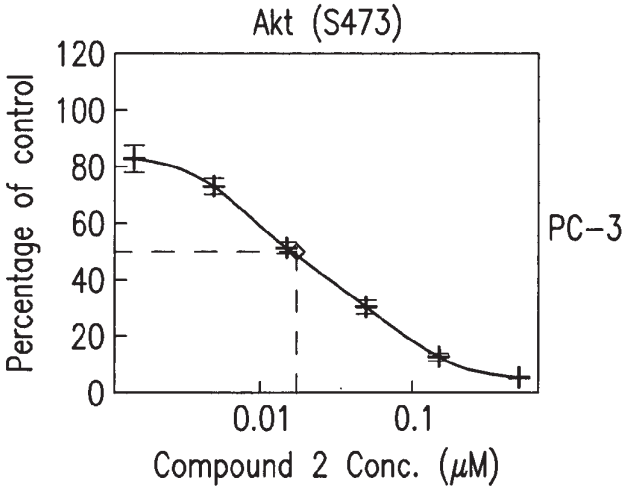


FIG. 8C

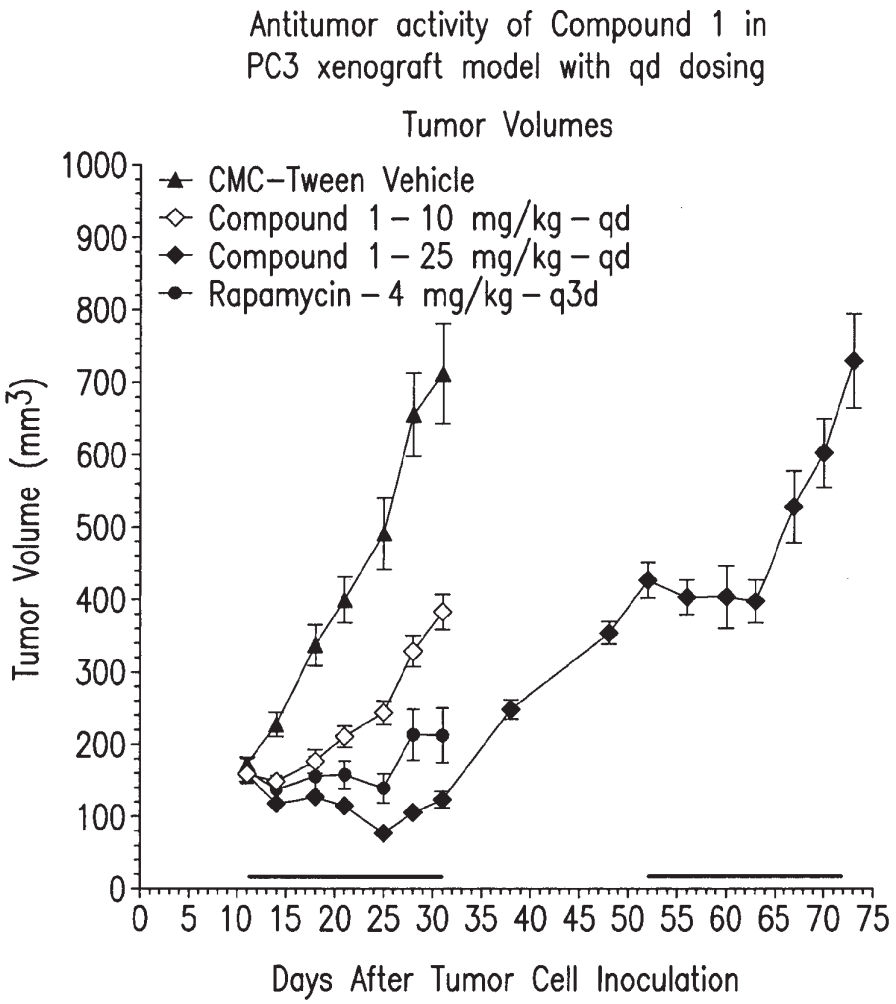

Antitumor activity of Compound 1 in
PC3 xenograft model with qd dosing
Tumor Volumes
CMC–Tween Vehicle
Compound 1 – 10 mg/kg – qd
Compound 1 – 25 mg/kg – qd
Rapamycin – 4 mg/kg – q3d
Tumor Volume (mm3)
1000
900
800
700
600
500
400
300
200
100
0
0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75
Days After Tumor Cell Inoculation

FIG. 9

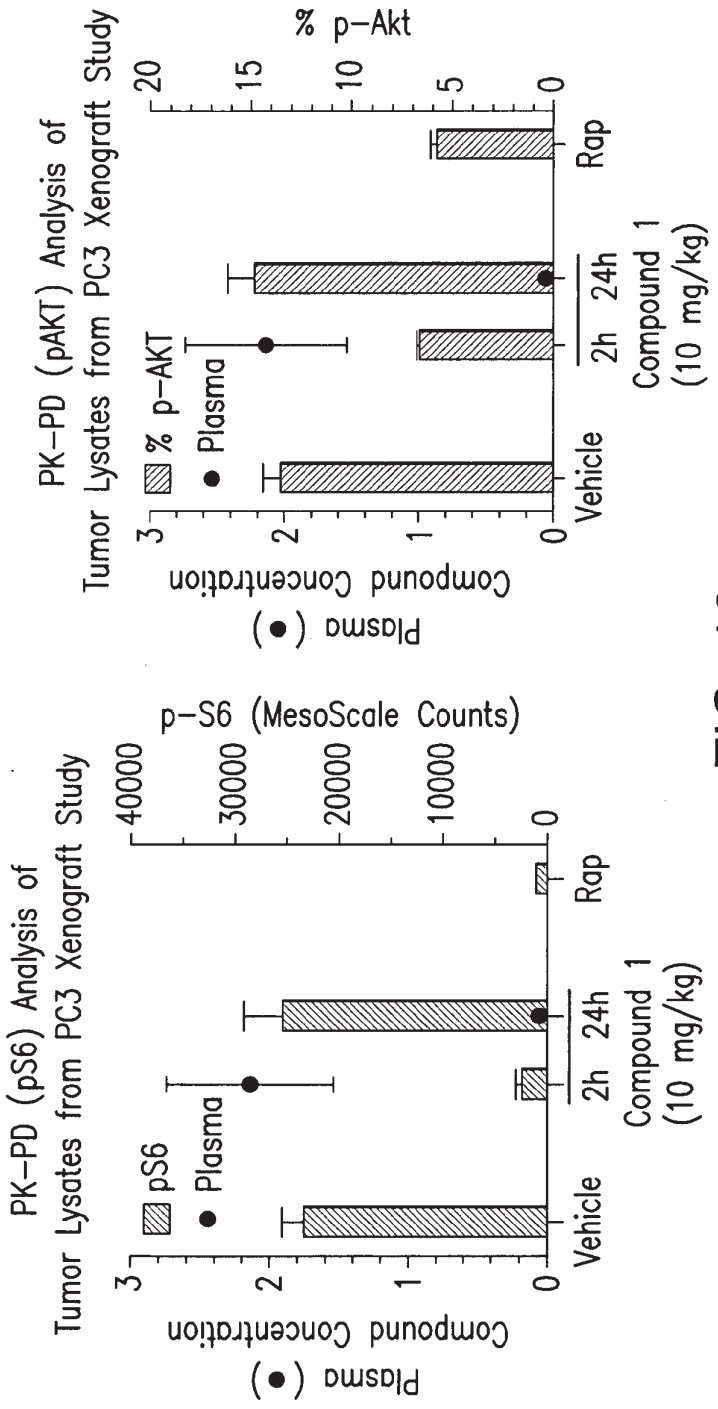

PK-PD (pS6) Analysis of
Tumor Lysates from PC3 Xenograft Study
p-S6 (MesoScale Counts)
40000
30000
20000
10000
0
pS6
Plasma
Plasma (●)
Compound Concentration
3
2
1
0
Vehicle
2h
24h
Rap
Compound 1
(10 mg/kg)
PK-PD (pAKT) Analysis of
Tumor Lysates from PC3 Xenograft Study
% p-Akt
20
15
10
5
0
% p-AKT
Plasma
Plasma (●)
Compound Concentration
3
2
1
0
Vehicle
2h
24h
Rap
Compound 1
(10 mg/kg)

FIG. 10

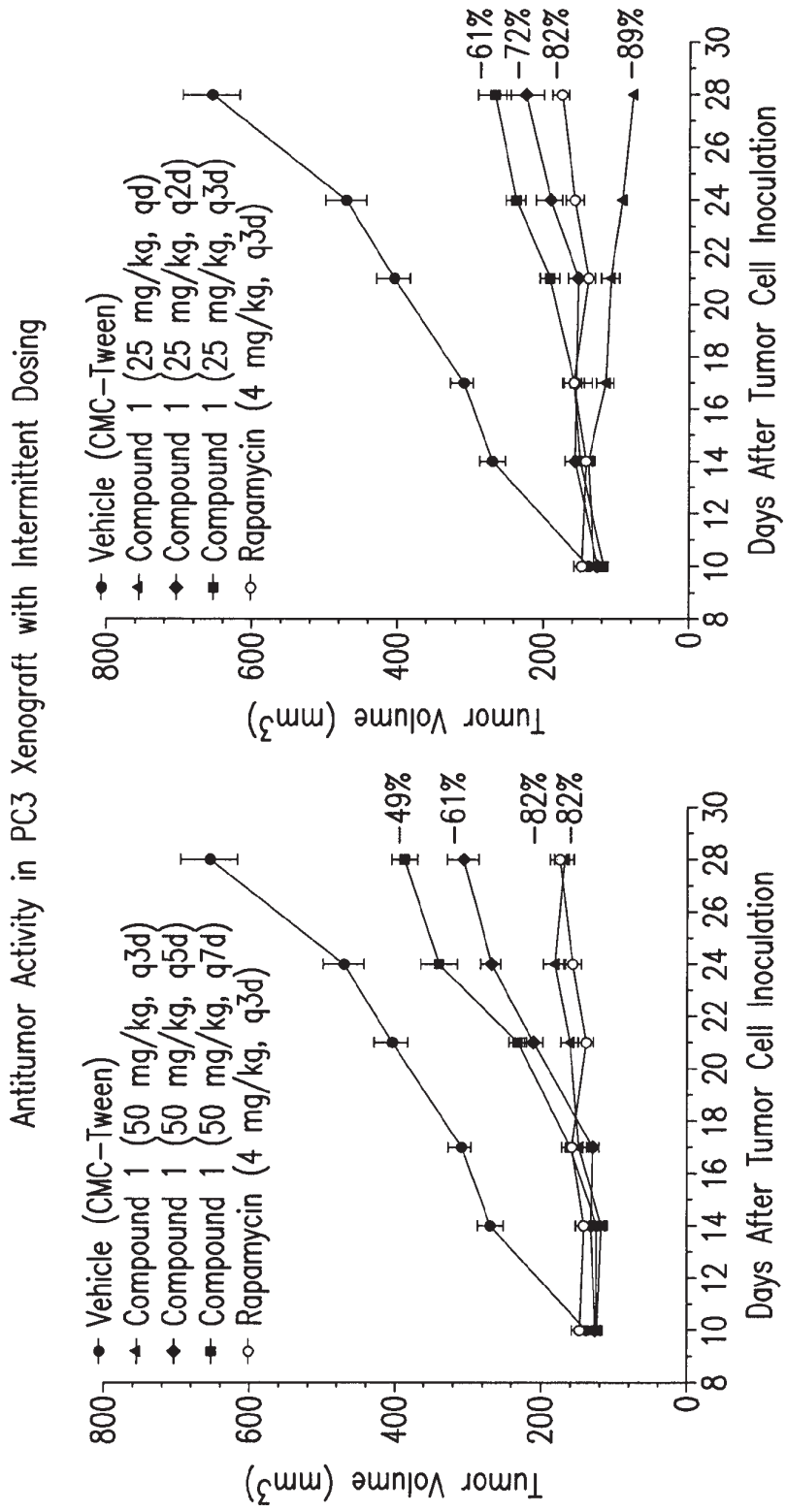

Antitumor Activity in PC3 Xenograft with Intermittent Dosing
Vehicle (CMC–Tween)
Compound 1 (50 mg/kg, q3d)
Compound 1 (50 mg/kg, q5d)
Compound 1 (50 mg/kg, q7d)
Rapamycin (4 mg/kg, q3d)
Tumor Volume (mm3)
Days After Tumor Cell Inoculation
0
200
400
600
800
8 10 12 14 16 18 20 22 24 26 28 30
–49%
–61%
–82%
–82%
Vehicle (CMC–Tween)
Compound 1 (25 mg/kg, qd)
Compound 1 (25 mg/kg, q2d)
Compound 1 (25 mg/kg, q3d)
Rapamycin (4 mg/kg, q3d)
–61%
–72%
–82%
–89%

FIG. 11

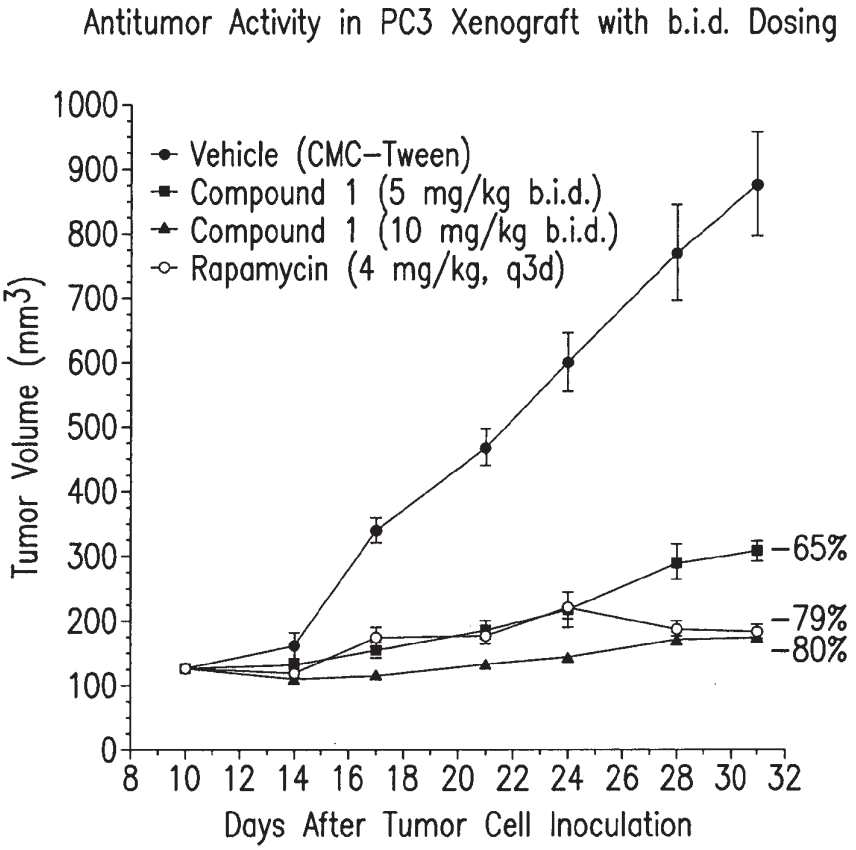

Antitumor Activity in PC3 Xenograft with b.i.d. Dosing
Vehicle (CMC–Tween)
Compound 1 (5 mg/kg b.i.d.)
Compound 1 (10 mg/kg b.i.d.)
Rapamycin (4 mg/kg, q3d)
Tumor Volume (mm3)
Days After Tumor Cell Inoculation
1000
900
800
700
600
500
400
300
200
100
0
8 10 12 14 16 18 20 22 24 26 28 30 32
–65%
–79%
–80%

FIG. 12

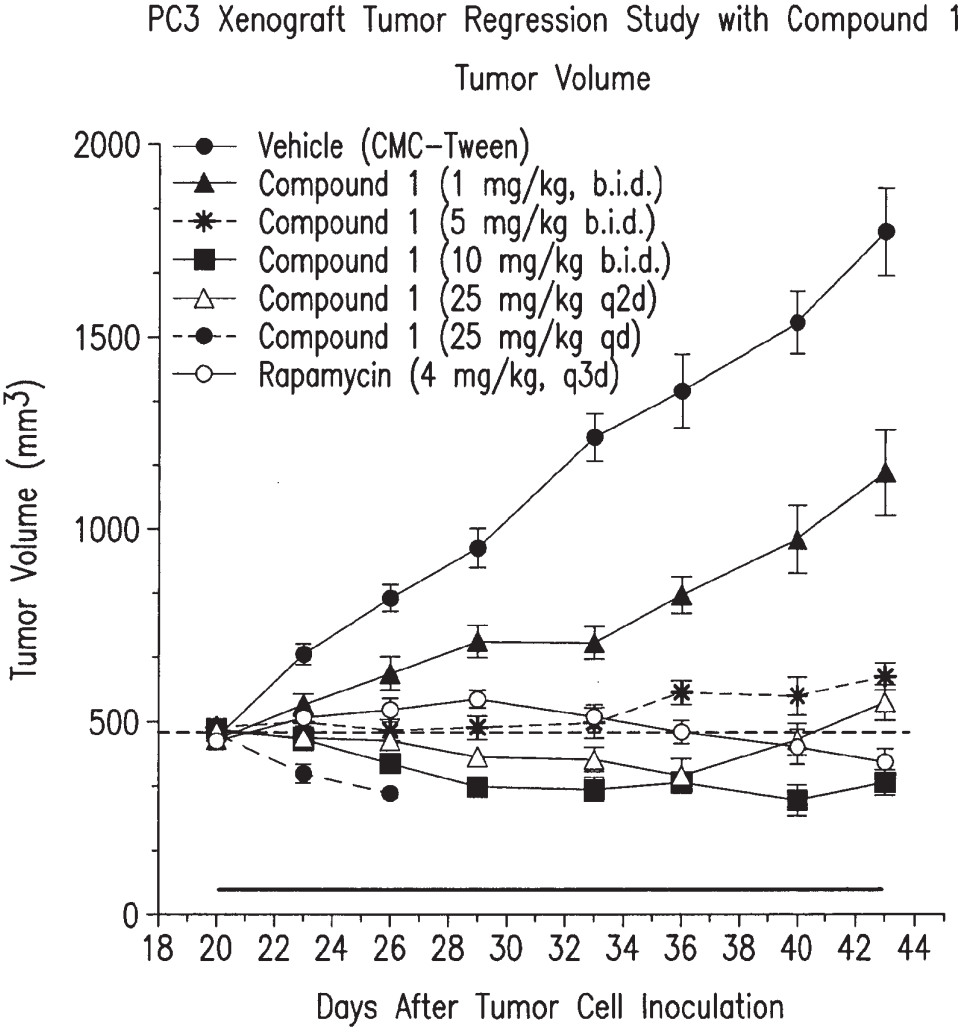

PC3 Xenograft Tumor Regression Study with Compound 1
Tumor Volume
Vehicle (CMC-Tween)
Compound 1 (1 mg/kg, b.i.d.)
Compound 1 (5 mg/kg b.i.d.)
Compound 1 (10 mg/kg b.i.d.)
Compound 1 (25 mg/kg q2d)
Compound 1 (25 mg/kg qd)
Rapamycin (4 mg/kg, q3d)
Tumor Volume (mm3)
2000
1500
1000
500
0
18 20 22 24 26 28 30 32 34 36 38 40 42 44
Days After Tumor Cell Inoculation

FIG. 13

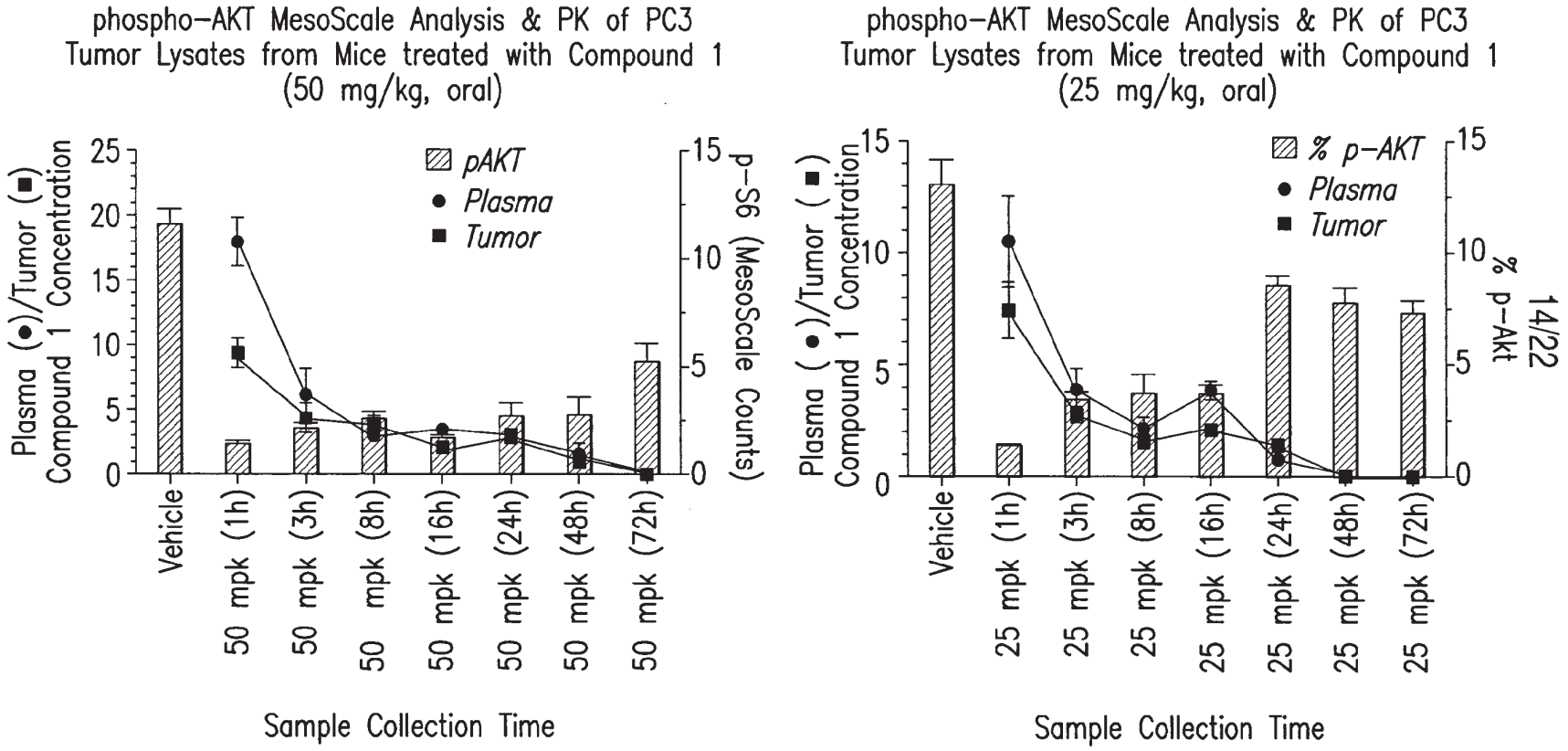

phospho–AKT MesoScale Analysis & PK of PC3
Tumor Lysates from Mice treated with Compound 1
(50 mg/kg, oral)
Plasma (●)/Tumor (■)
Compound 1 Concentration
pAKT
Plasma
Tumor
p–S6 (MesoScale Counts)
Vehicle
50 mpk (1h)
50 mpk (3h)
50 mpk (8h)
50 mpk (16h)
50 mpk (24h)
50 mpk (48h)
50 mpk (72h)
Sample Collection Time
phospho–AKT MesoScale Analysis & PK of PC3
Tumor Lysates from Mice treated with Compound 1
(25 mg/kg, oral)
Plasma (●)/Tumor (■)
Compound 1 Concentration
% p–AKT
Plasma
Tumor
% p–Akt
Vehicle
25 mpk (1h)
25 mpk (3h)
25 mpk (8h)
25 mpk (16h)
25 mpk (24h)
25 mpk (48h)
25 mpk (72h)
Sample Collection Time

FIG. 14

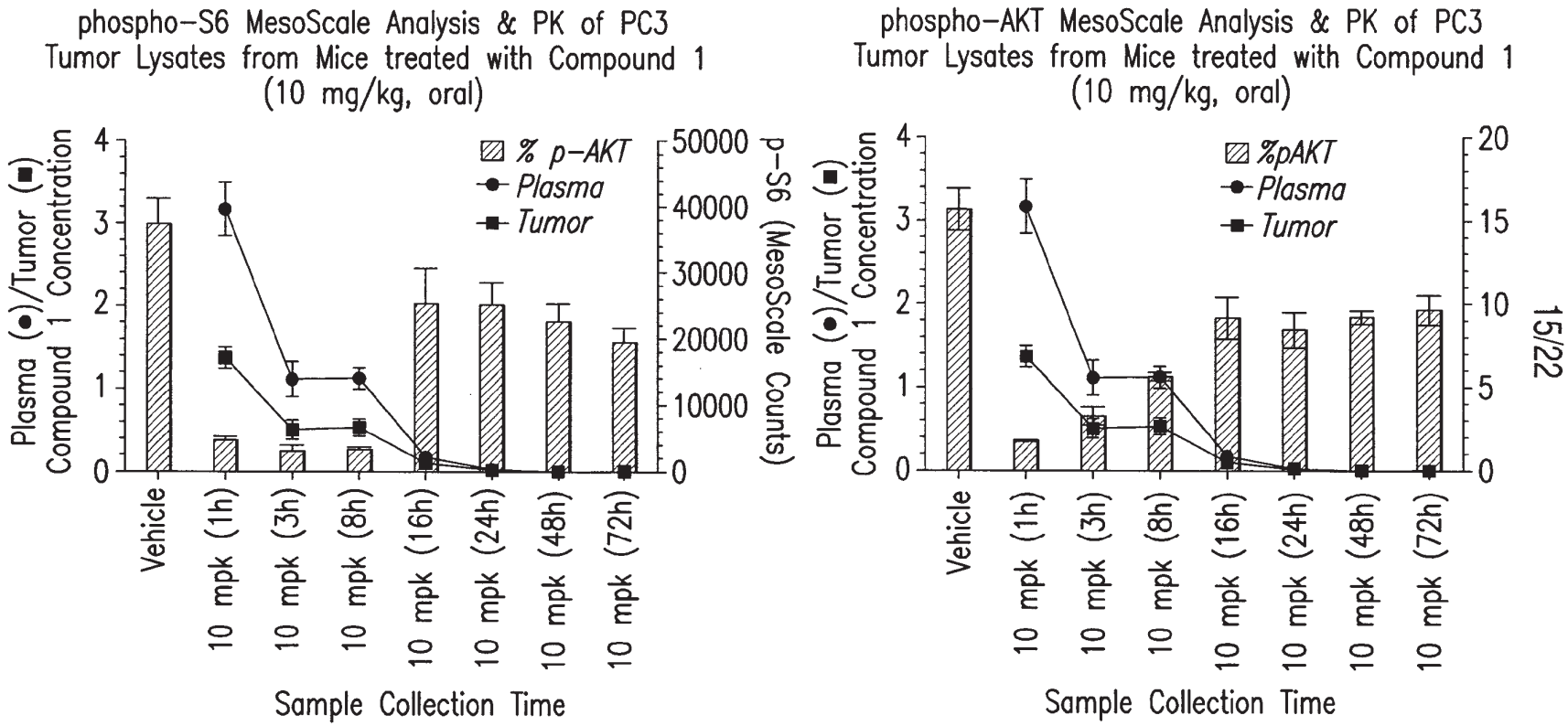

phospho-S6 MesoScale Analysis & PK of PC3
Tumor Lysates from Mice treated with Compound 1
(10 mg/kg, oral)
Plasma (●)/Tumor (■)
Compound 1 Concentration
% p-AKT
Plasma
Tumor
p-S6 (MesoScale Counts)
Vehicle
10 mpk (1h)
10 mpk (3h)
10 mpk (8h)
10 mpk (16h)
10 mpk (24h)
10 mpk (48h)
10 mpk (72h)
Sample Collection Time
phospho-AKT MesoScale Analysis & PK of PC3
Tumor Lysates from Mice treated with Compound 1
(10 mg/kg, oral)
Plasma (●)/Tumor (■)
Compound 1 Concentration
%pAKT
Plasma
Tumor
Vehicle
10 mpk (1h)
10 mpk (3h)
10 mpk (8h)
10 mpk (16h)
10 mpk (24h)
10 mpk (48h)
10 mpk (72h)
Sample Collection Time

FIG. 15

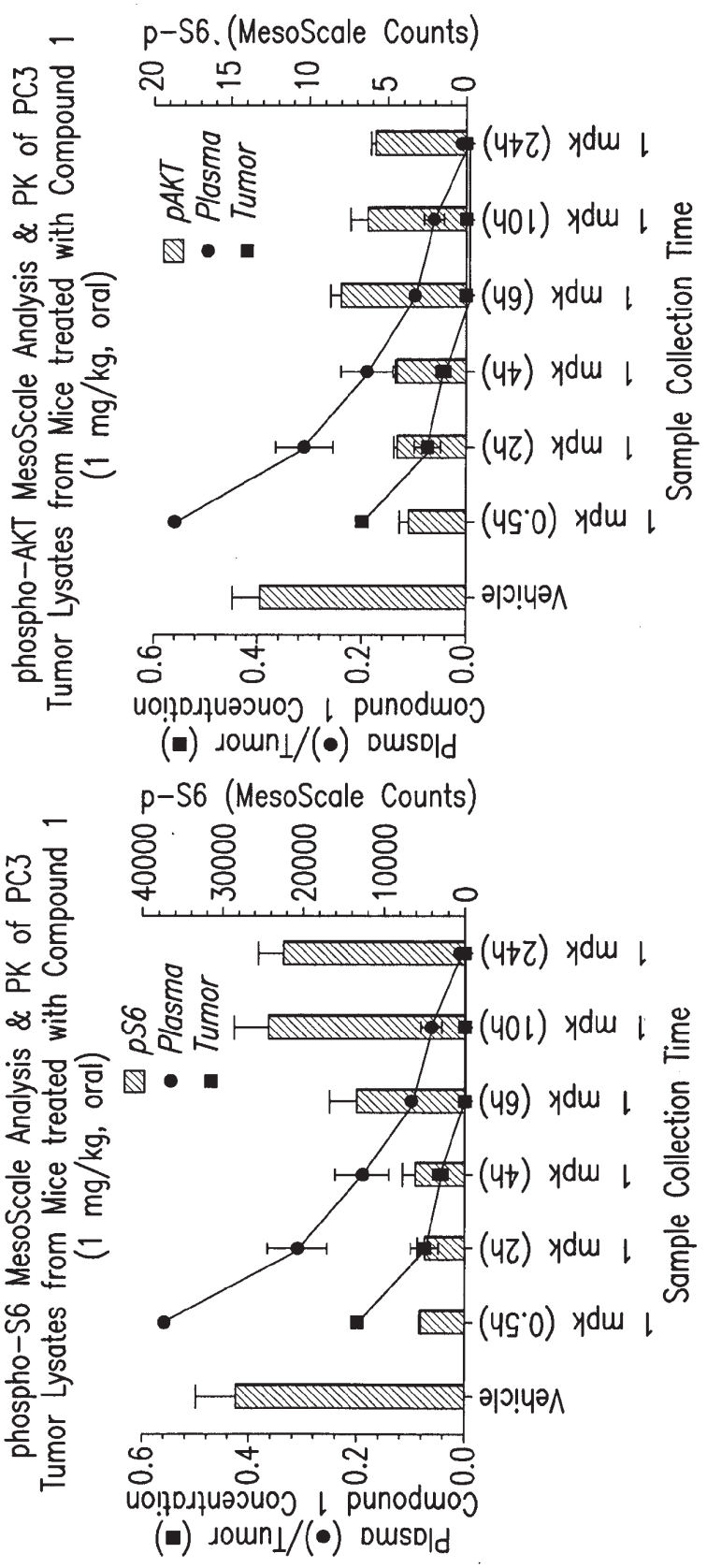

phospho-S6 MesoScale Analysis & PK of PC3
Tumor Lysates from Mice treated with Compound 1
(1 mg/kg, oral)
p-S6 (MesoScale Counts)
40000
30000
20000
10000
0
pS6
Plasma
Tumor
Plasma (●)/Tumor (■)
Compound 1 Concentration
0.6
0.4
0.2
0.0
Vehicle
1 mpk (0.5h)
1 mpk (2h)
1 mpk (4h)
1 mpk (6h)
1 mpk (10h)
1 mpk (24h)
Sample Collection Time
phospho-AKT MesoScale Analysis & PK of PC3
Tumor Lysates from Mice treated with Compound 1
(1 mg/kg, oral)
p-S6 (MesoScale Counts)
20
15
10
5
0
pAKT
Plasma
Tumor
Plasma (●)/Tumor (■)
Compound 1 Concentration
0.6
0.4
0.2
0.0
Vehicle
1 mpk (0.5h)
1 mpk (2h)
1 mpk (4h)
1 mpk (6h)
1 mpk (10h)
1 mpk (24h)
Sample Collection Time

FIG. 16

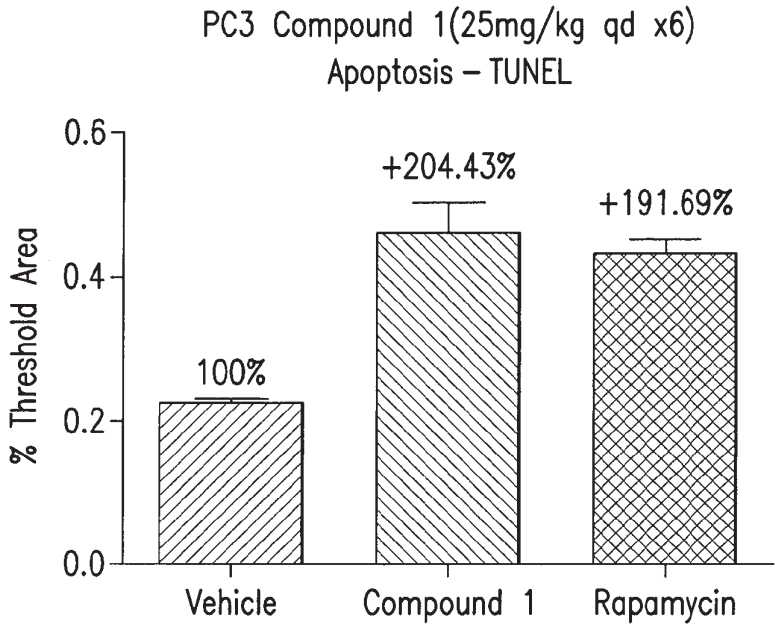

PC3 Compound 1(25mg/kg qd x6)
Apoptosis – TUNEL
% Threshold Area
0.6
0.4
0.2
0.0
100%
+204.43%
+191.69%
Vehicle
Compound 1
Rapamycin

FIG. 17

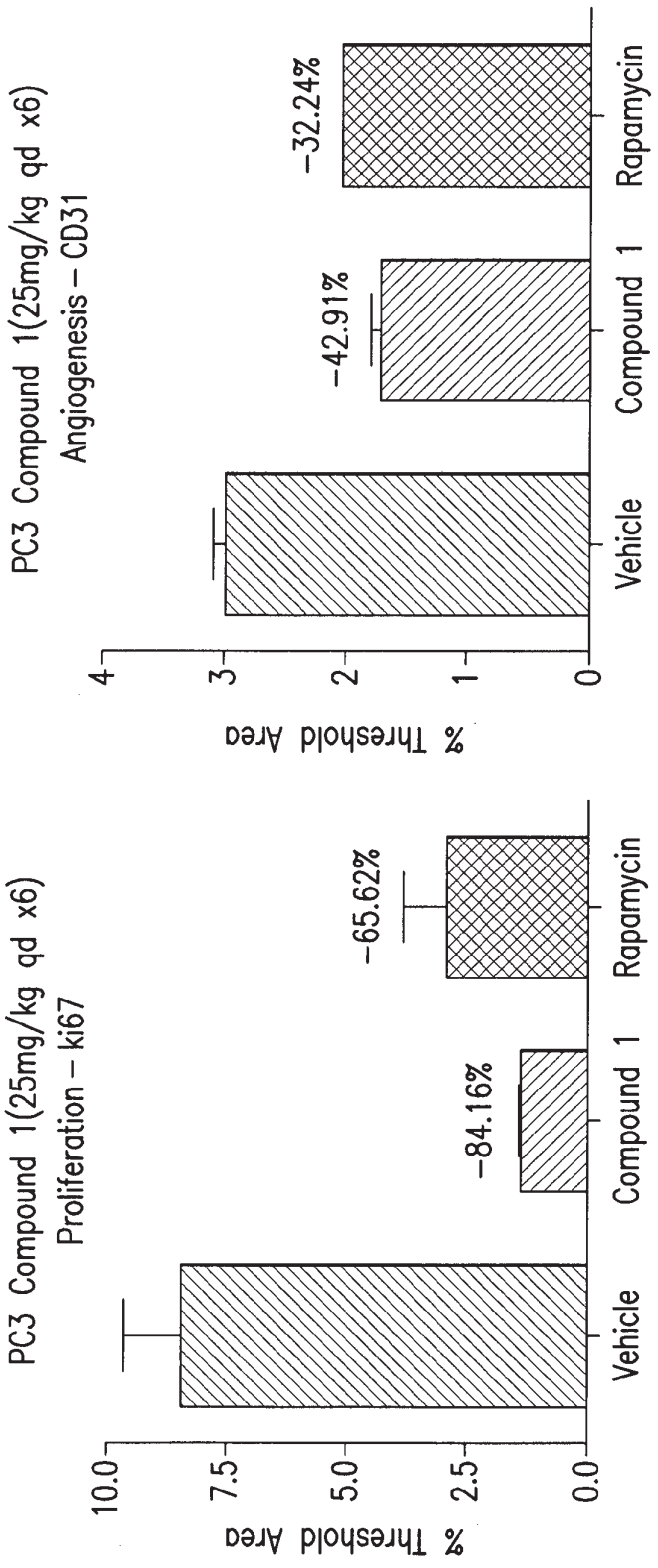

PC3 Compound 1(25mg/kg qd x6)
Proliferation – ki67
% Threshold Area
10.0
7.5
5.0
2.5
0.0
Vehicle
Compound 1
Rapamycin
-84.16%
-65.62%
PC3 Compound 1(25mg/kg qd x6)
Angiogenesis – CD31
% Threshold Area
4
3
2
1
0
Vehicle
Compound 1
Rapamycin
-42.91%
-32.24%

FIG. 18

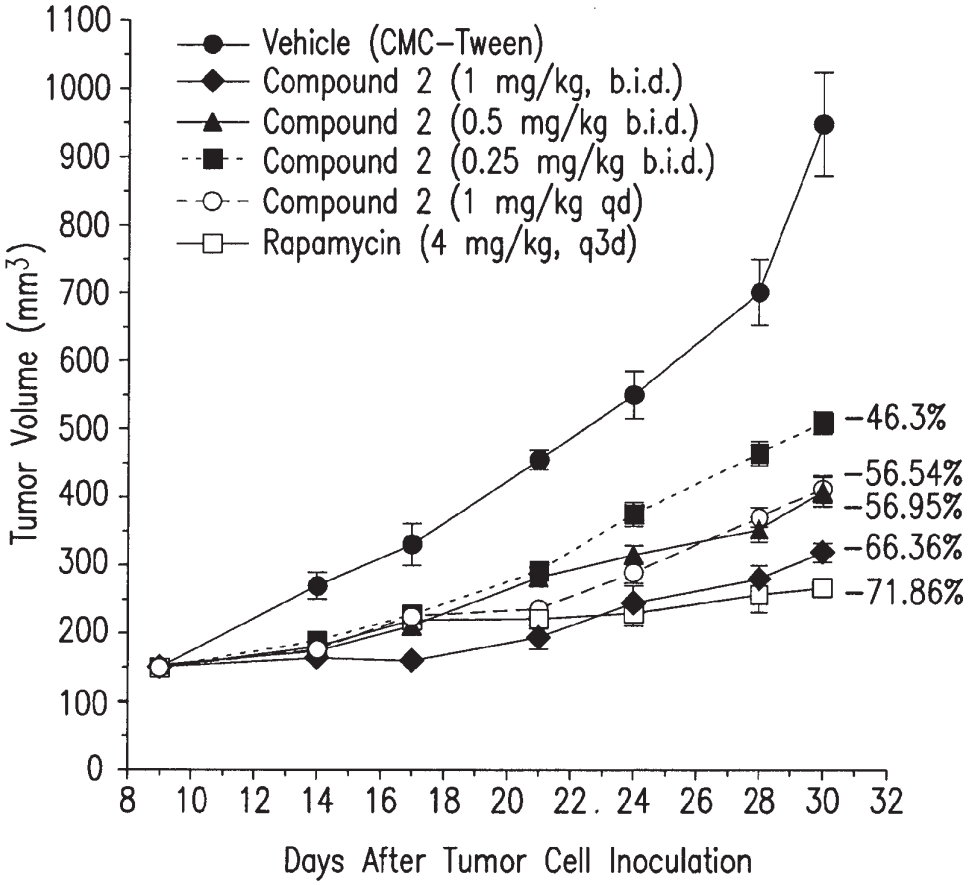

Vehicle (CMC–Tween)
Compound 2 (1 mg/kg, b.i.d.)
Compound 2 (0.5 mg/kg b.i.d.)
Compound 2 (0.25 mg/kg b.i.d.)
Compound 2 (1 mg/kg qd)
Rapamycin (4 mg/kg, q3d)
-46.3%
-56.54%
-56.95%
-66.36%
-71.86%
Tumor Volume (mm3)
Days After Tumor Cell Inoculation
0
100
200
300
400
500
600
700
800
900
1000
1100
8
10
12
14
16
18
20
22
24
26
28
30
32

FIG. 19

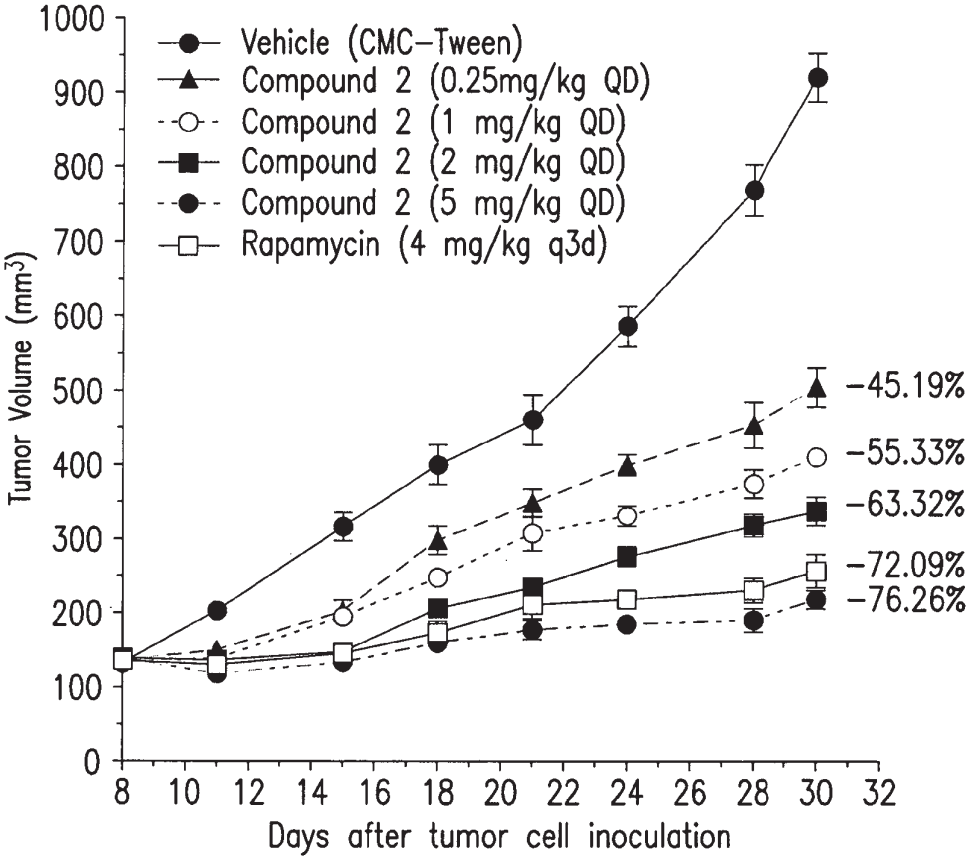

Vehicle (CMC–Tween)
Compound 2 (0.25mg/kg QD)
Compound 2 (1 mg/kg QD)
Compound 2 (2 mg/kg QD)
Compound 2 (5 mg/kg QD)
Rapamycin (4 mg/kg q3d)
Tumor Volume (mm3)
Days after tumor cell inoculation
-45.19%
-55.33%
-63.32%
-72.09%
-76.26%
0
100
200
300
400
500
600
700
800
900
1000
8
10
12
14
16
18
20
22
24
26
28
30
32

FIG. 20

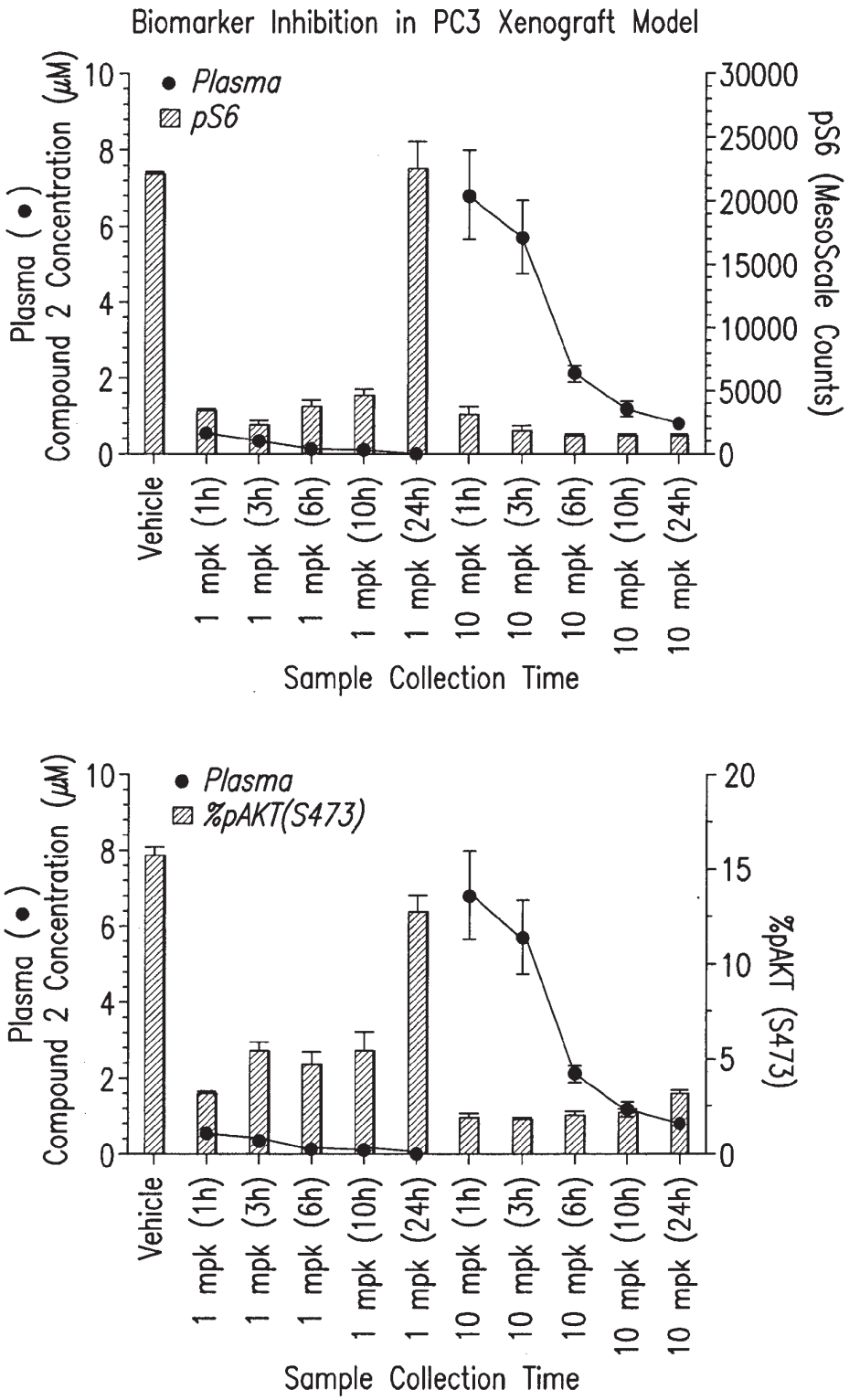

Biomarker Inhibition in PC3 Xenograft Model
Plasma
pS6
Plasma (•) Compound 2 Concentration (μM)
pS6 (MesoScale Counts)
0
2
4
6
8
10
0
5000
10000
15000
20000
25000
30000
Vehicle
1 mpk (1h)
1 mpk (3h)
1 mpk (6h)
1 mpk (10h)
1 mpk (24h)
10 mpk (1h)
10 mpk (3h)
10 mpk (6h)
10 mpk (10h)
10 mpk (24h)
Sample Collection Time
Plasma
%pAKT(S473)
Plasma (•) Compound 2 Concentration (μM)
%pAKT (S473)
0
5
10
15
20
Vehicle
1 mpk (1h)
1 mpk (3h)
1 mpk (6h)
1 mpk (10h)
1 mpk (24h)
10 mpk (1h)
10 mpk (3h)
10 mpk (6h)
10 mpk (10h)
10 mpk (24h)
Sample Collection Time

FIG. 21

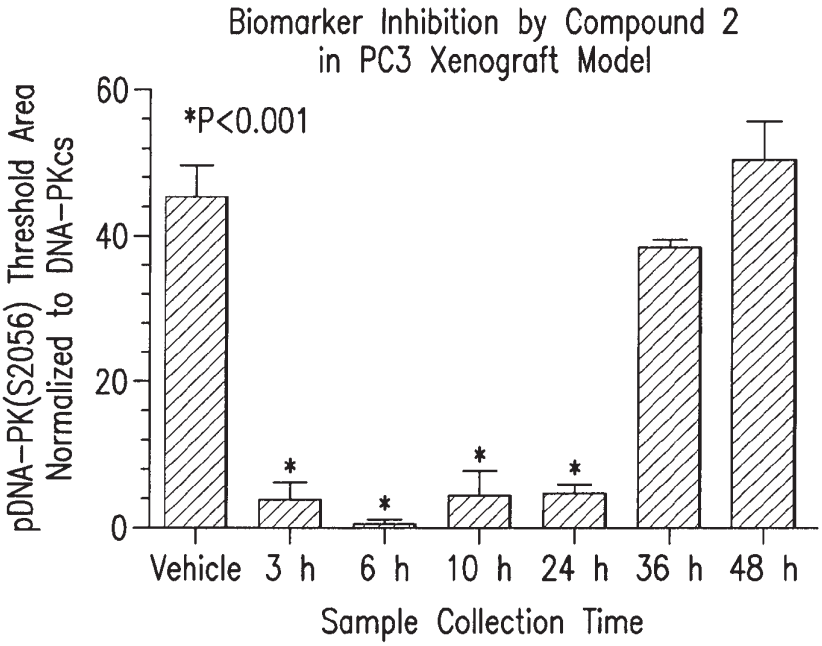

Biomarker Inhibition by Compound 2
in PC3 Xenograft Model
pDNA-PK(S2056) Threshold Area
Normalized to DNA-PKcs
60
40
20
0
*P<0.001
*
*
*
*
Vehicle
3 h
6 h
10 h
24 h
36 h
48 h
Sample Collection Time

FIG. 22