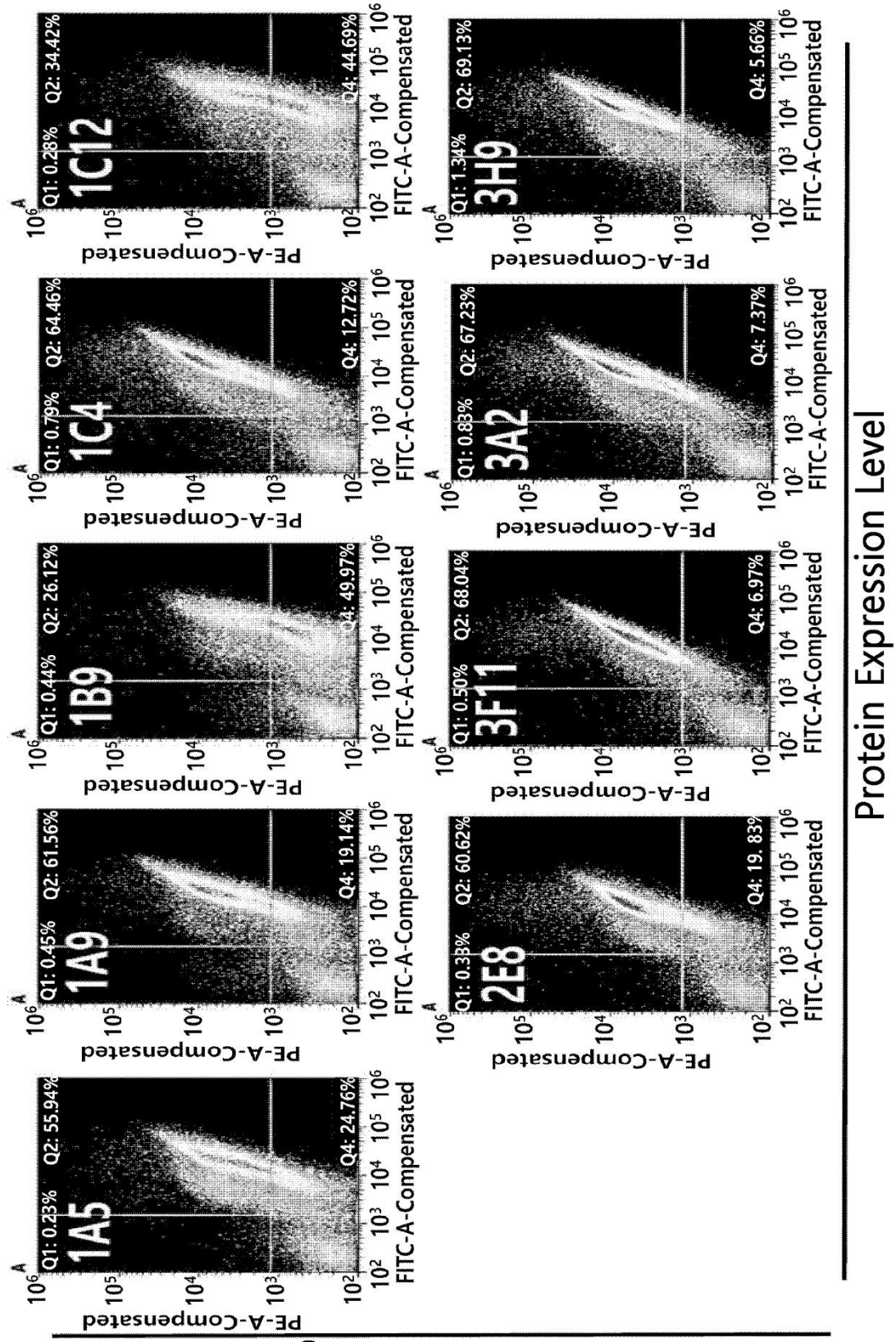
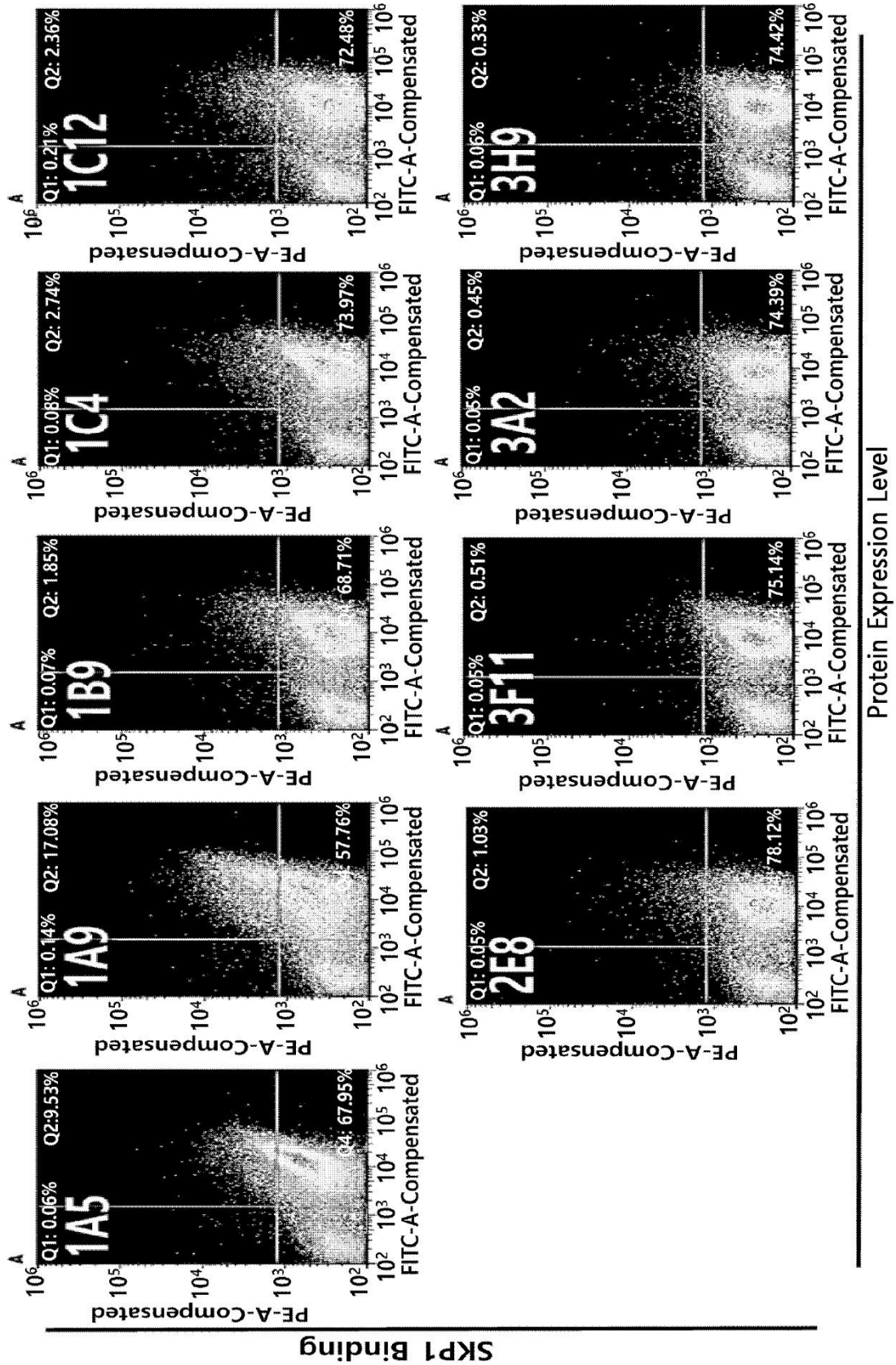
DRAWINGS

[FIG. 1]

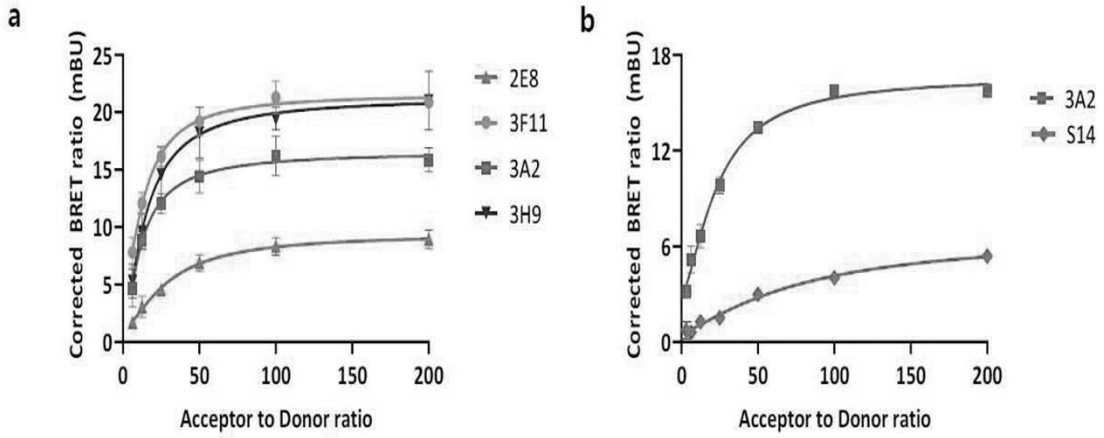
[FIG. 2a]


SOX2 Binding
Protein Expression Level
1A5
Q1: 0.23%
Q2: 55.94%
Q4: 24.76%
1A9
Q1: 0.45%
Q2: 61.56%
Q4: 19.14%
1B9
Q1: 0.44%
Q2: 26.12%
Q4: 49.97%
1C4
Q1: 0.79%
Q2: 64.46%
Q4: 12.72%
1C12
Q1: 0.28%
Q2: 34.42%
Q4: 44.69%
2E8
Q1: 0.3%
Q2: 60.62%
Q4: 19. 83%
3A2
Q1: 0.83%
Q2: 67.23%
Q4: 7.37%
3F11
Q1: 0.50%
Q2: 68.04%
Q4: 6.97%
3H9
Q1: 1.34%
Q2: 69.13%
Q4: 5.66%
PE-A-Compensated
FITC-A-Compensated

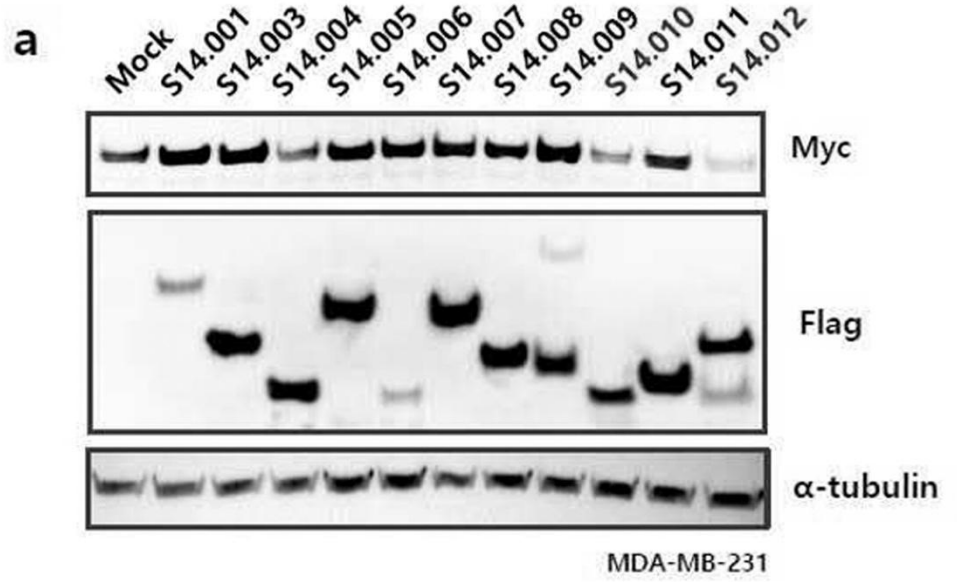
[FIG. 2b]

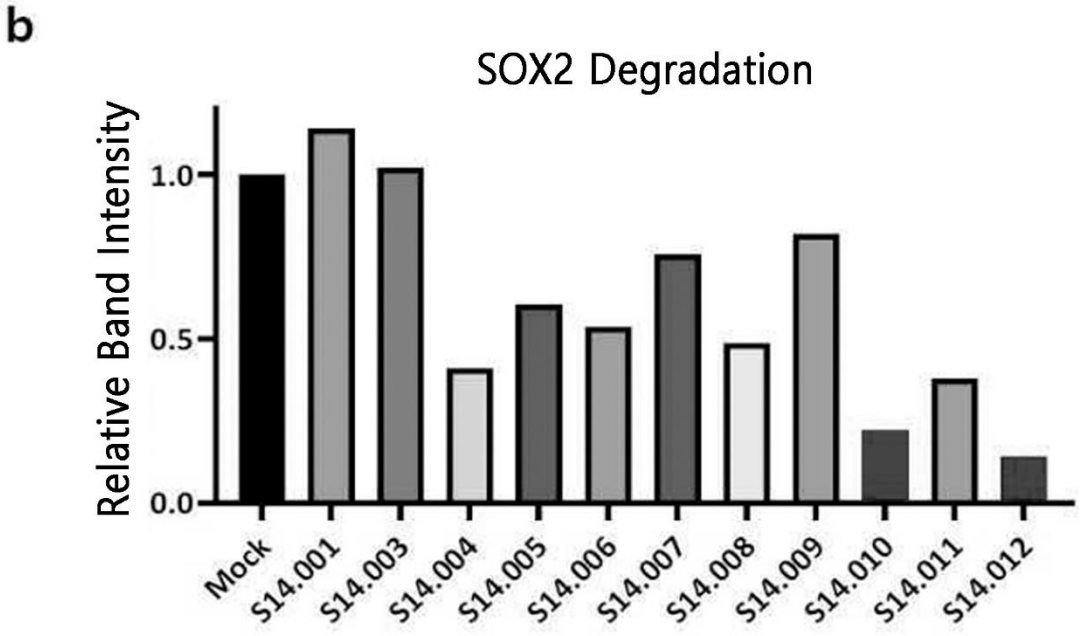

SKP1 Binding
Protein Expression Level
1A5
Q1: 0.06%
Q2:9.53%
Q4: 67.95%
1A9
Q1: 0.14%
Q2: 17.08%
57.76%
1B9
Q1: 0.07%
Q2: 1.85%
68.71%
1C4
Q1: 0.08%
Q2: 2.74%
73.97%
1C12
Q1: 0.21%
Q2: 2.36%
72.48%
2E8
Q1: 0.05%
Q2: 1.03%
78.12%
3F11
Q1: 0.05%
Q2: 0.51%
75.14%
3A2
Q1: 0.05%
Q2: 0.45%
74.39%
3H9
Q1: 0.06%
Q2: 0.33%
74.42%
PE-A-Compensated
FITC-A-Compensated

[FIG. 3]

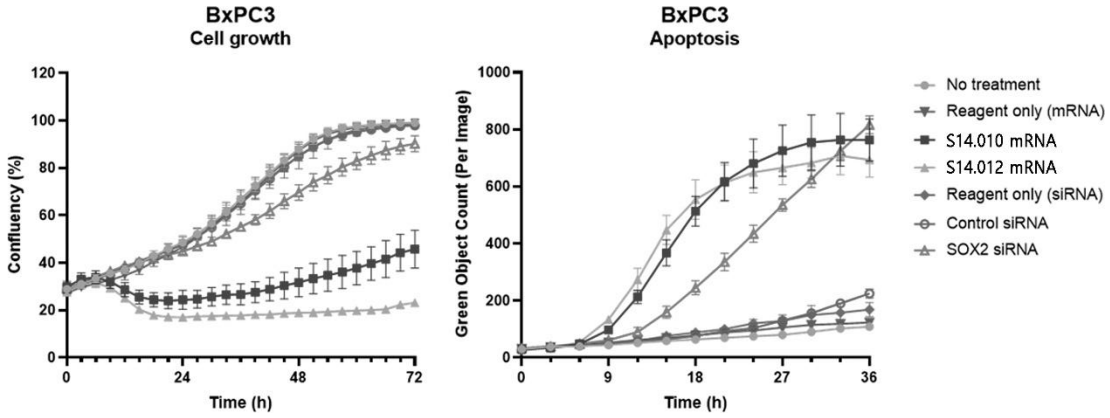

a
Corrected BRET ratio (mBU)
25
20
15
10
5
0
0
50
100
150
200
Acceptor to Donor ratio
2E8
3F11
3A2
3H9
b
Corrected BRET ratio (mBU)
18
12
6
0
0
50
100
150
200
Acceptor to Donor ratio
3A2
S14

[FIG. 4]

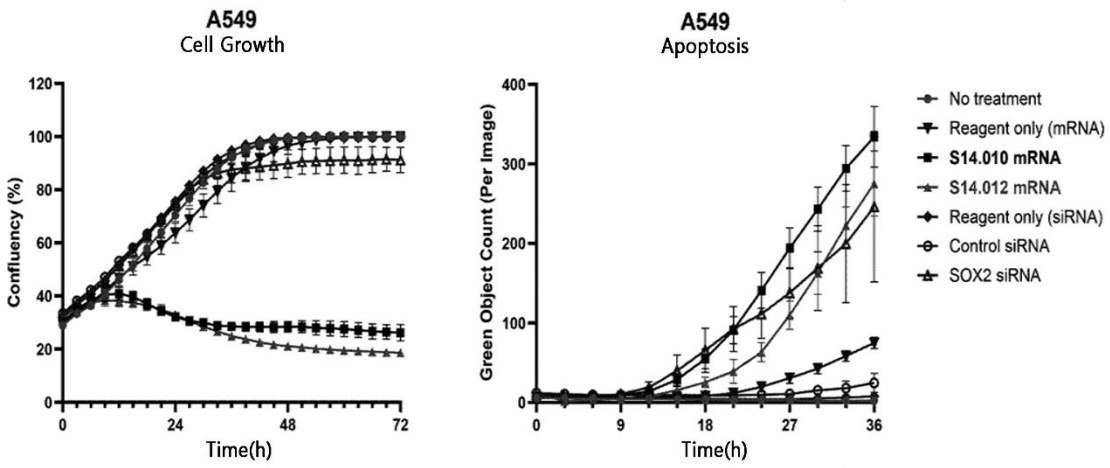

a
Mock
S14.001
S14.003
S14.004
S14.005
S14.006
S14.007
S14.008
S14.009
S14.010
S14.011
S14.012
Myc
Flag
α-tubulin
MDA-MB-231


b
SOX2 Degradation
Relative Band Intensity
1.0
0.5
0.0
Mock
S14.001
S14.003
S14.004
S14.005
S14.006
S14.007
S14.008
S14.009
S14.010
S14.011
S14.012

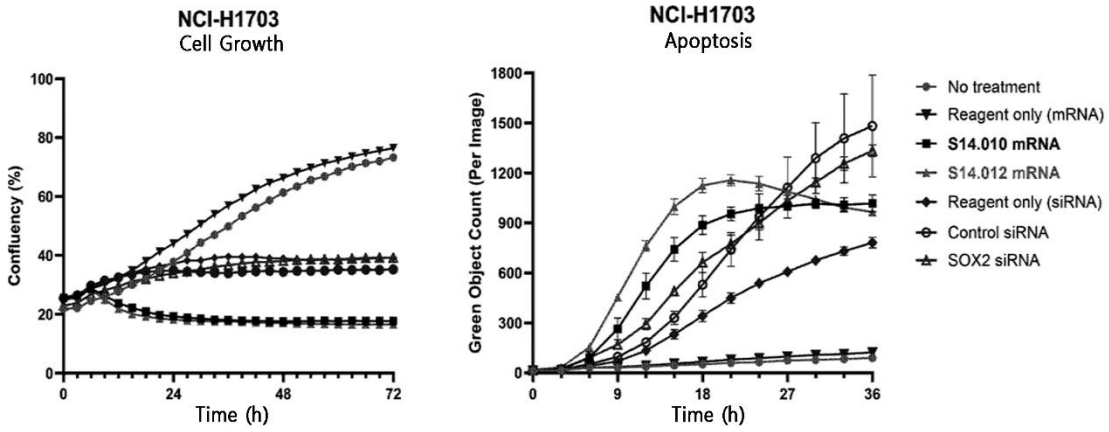
[FIG. 5a]


BxPC3
Cell growth
Confluency (%)
Time (h)
BxPC3
Apoptosis
Green Object Count (Per Image)
Time (h)
No treatment
Reagent only (mRNA)
S14.010 mRNA
S14.012 mRNA
Reagent only (siRNA)
Control siRNA
SOX2 siRNA

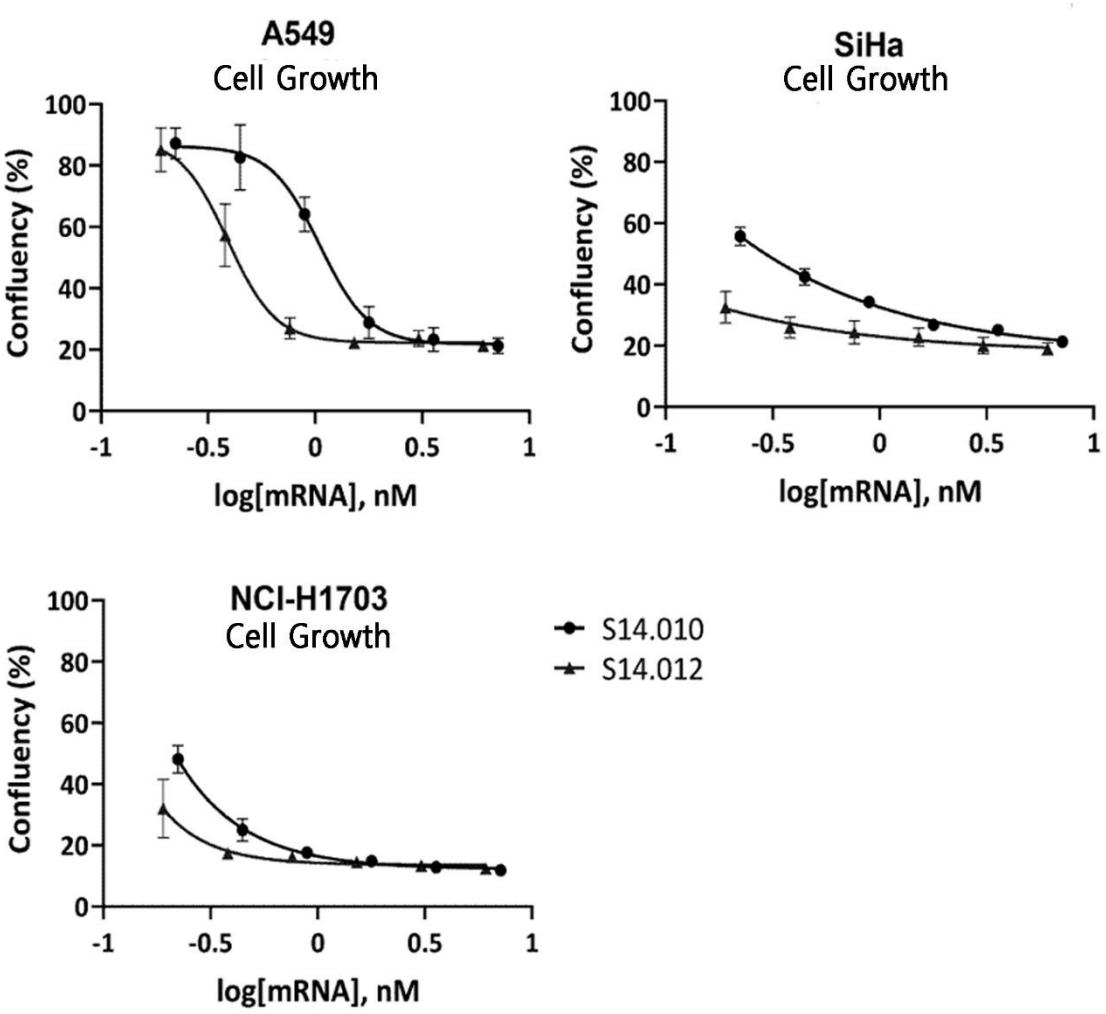
[FIG. 5b]


A549
Cell Growth
Confluency (%)
Time(h)
A549
Apoptosis
Green Object Count (Per Image)
Time(h)
No treatment
Reagent only (mRNA)
S14.010 mRNA
S14.012 mRNA
Reagent only (siRNA)
Control siRNA
SOX2 siRNA

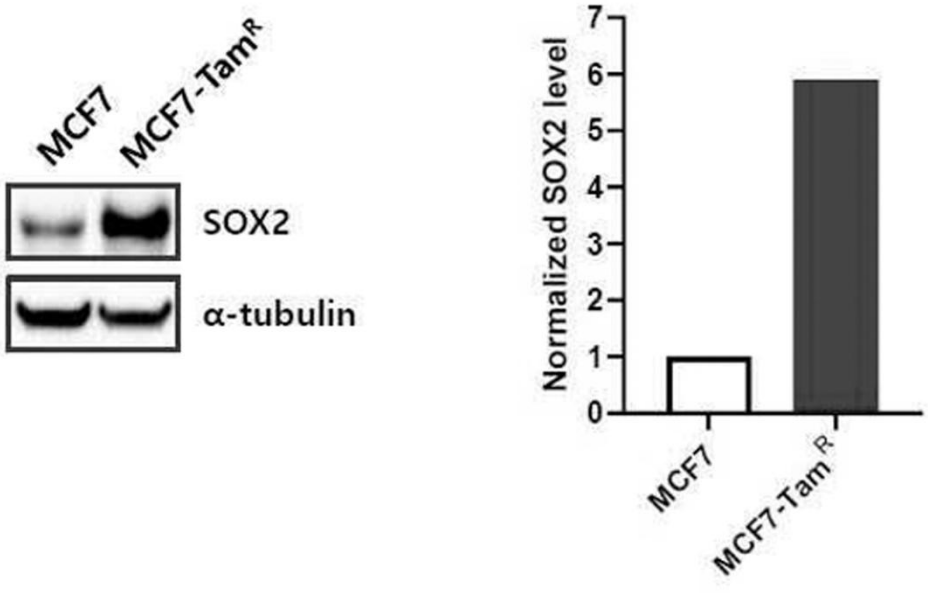
[FIG. 5c]


NCI-H1703
Cell Growth
Confluency (%)
Time (h)
NCI-H1703
Apoptosis
Green Object Count (Per Image)
Time (h)
No treatment
Reagent only (mRNA)
S14.010 mRNA
S14.012 mRNA
Reagent only (siRNA)
Control siRNA
SOX2 siRNA

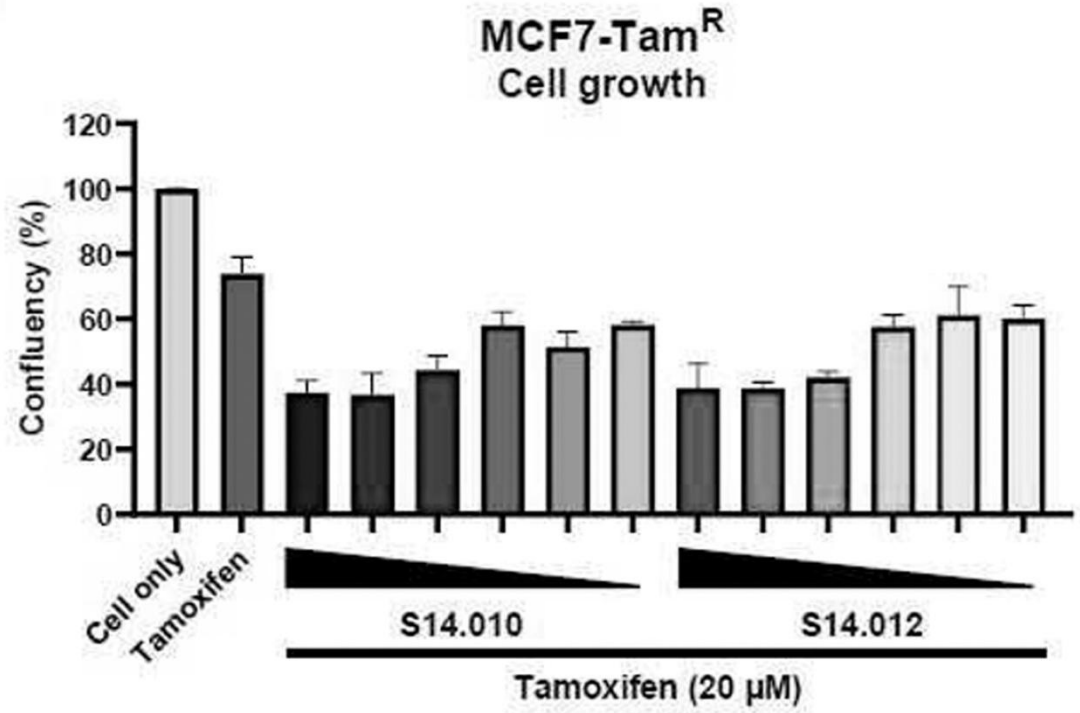
[FIG. 6]

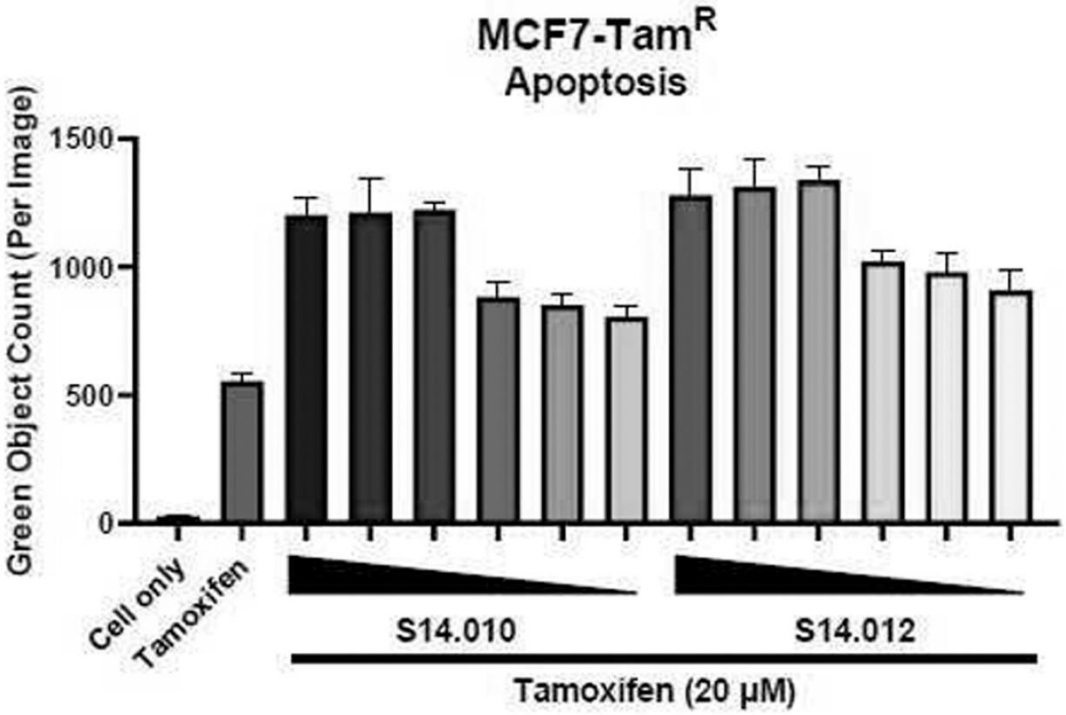

A549
Cell Growth
Confluency (%)
log[mRNA], nM
SiHa
Cell Growth
Confluency (%)
log[mRNA], nM
NCI-H1703
Cell Growth
Confluency (%)
log[mRNA], nM
S14.010
S14.012

[FIG. 7a]

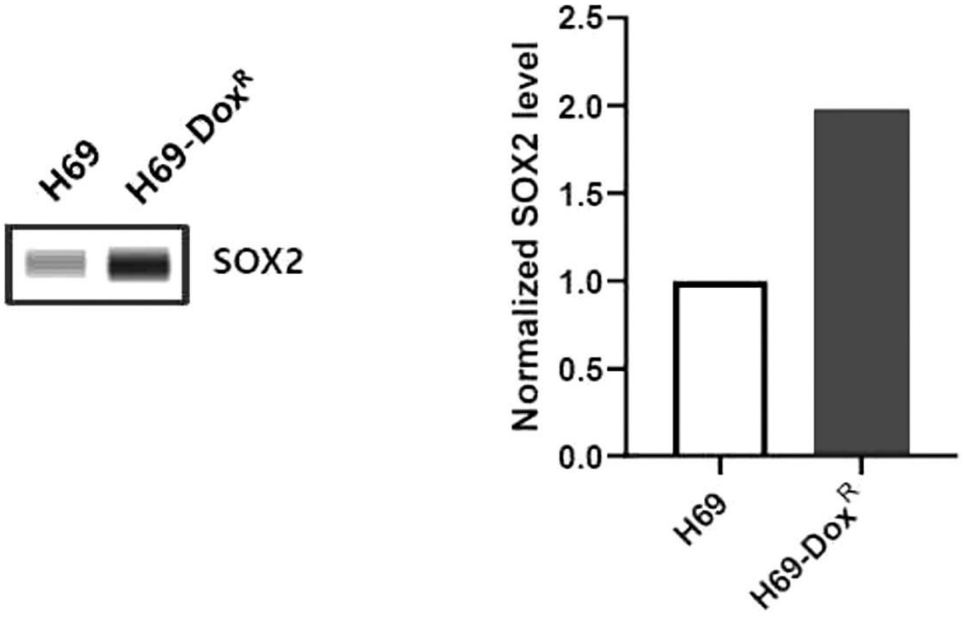

MCF7
MCF7-Tam^R
SOX2
α-tubulin
Normalized SOX2 level
0
1
2
3
4
5
6
7
MCF7
MCF7-Tam^R

[FIG. 7b]

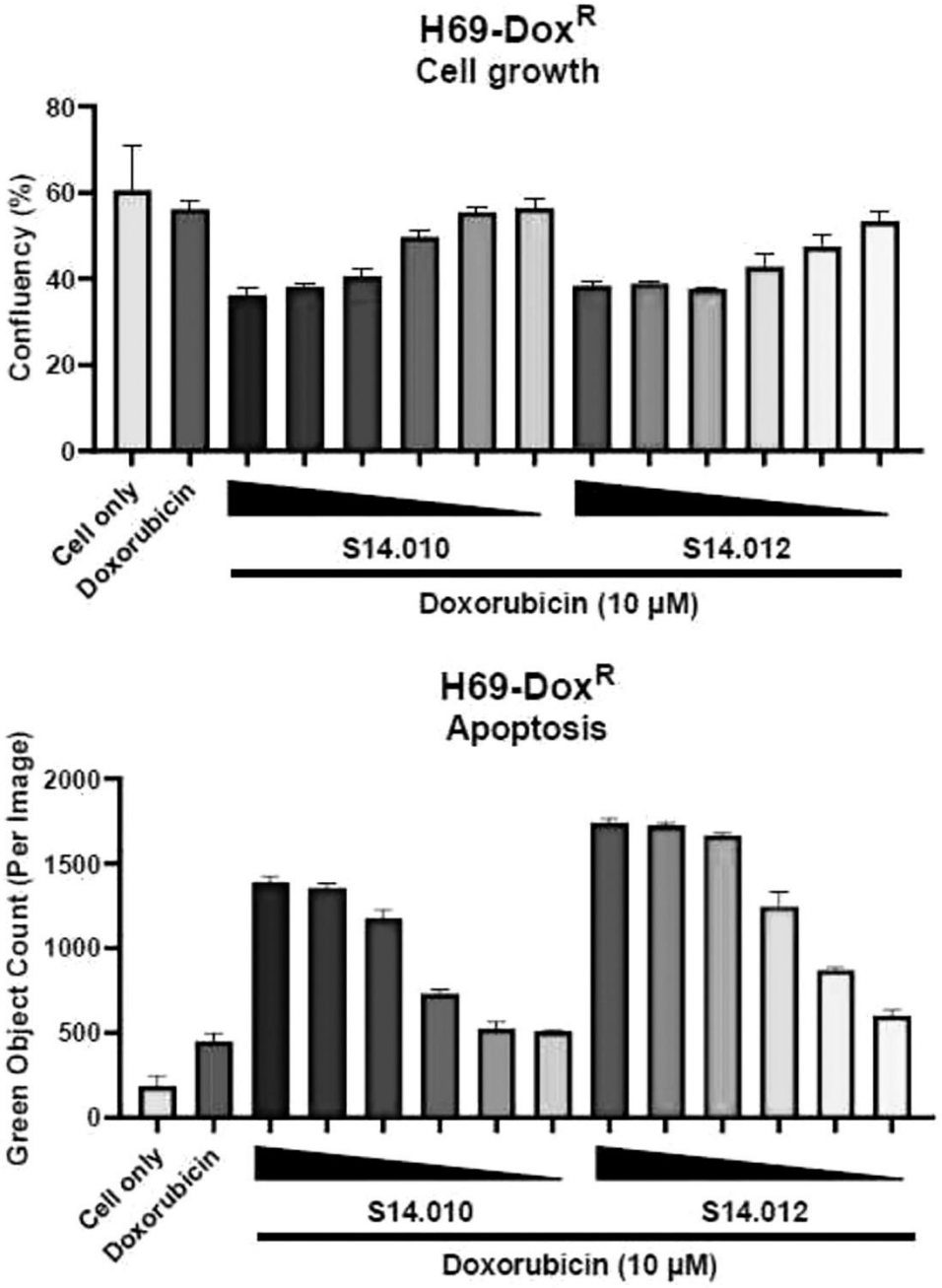

MCF7-Tam^R
Cell growth
Confluency (%)
120
100
80
60
40
20
0
Cell only
Tamoxifen
S14.010
S14.012
Tamoxifen (20 μM)


MCF7-Tam^R
Apoptosis
Green Object Count (Per Image)
1500
1000
500
0
Cell only
Tamoxifen
S14.010
S14.012
Tamoxifen (20 μM)

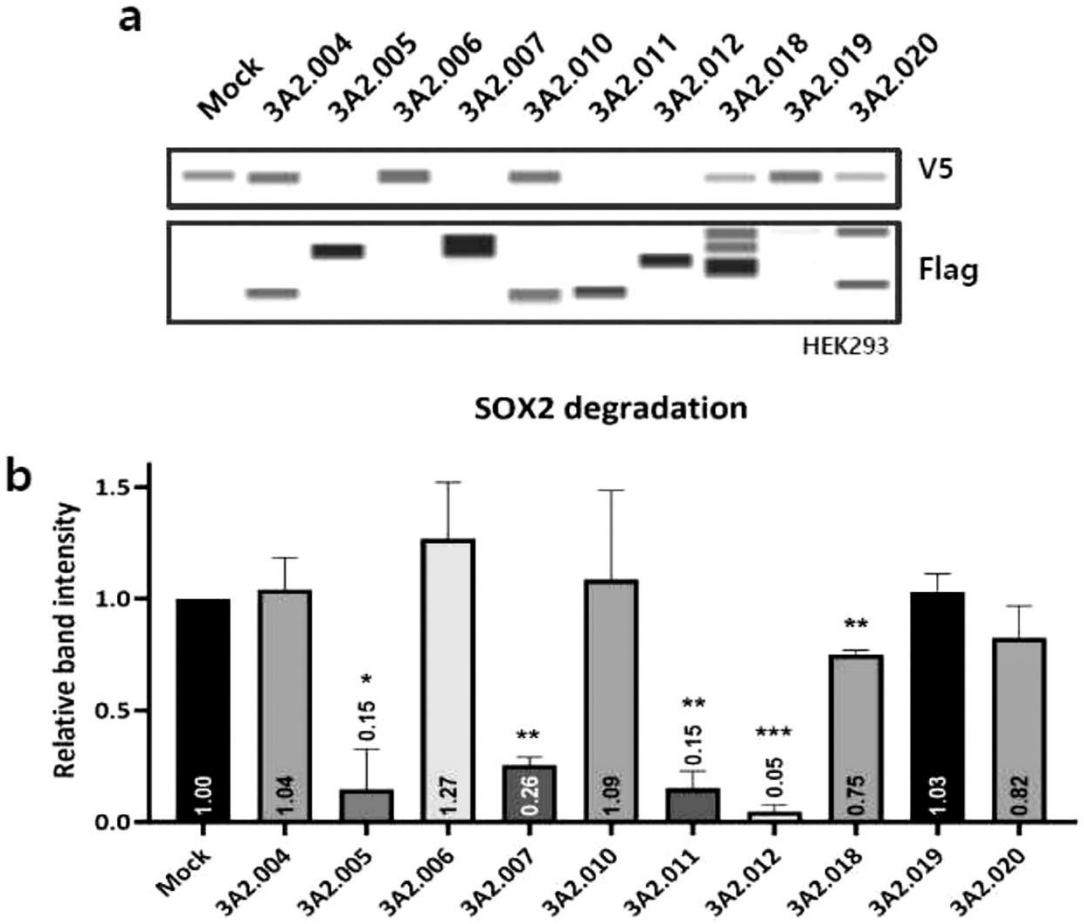
[FIG. 8a]


H69
H69-Dox^R
SOX2
Normalized SOX2 level
2.5
2.0
1.5
1.0
0.5
0.0
H69
H69-Dox^R

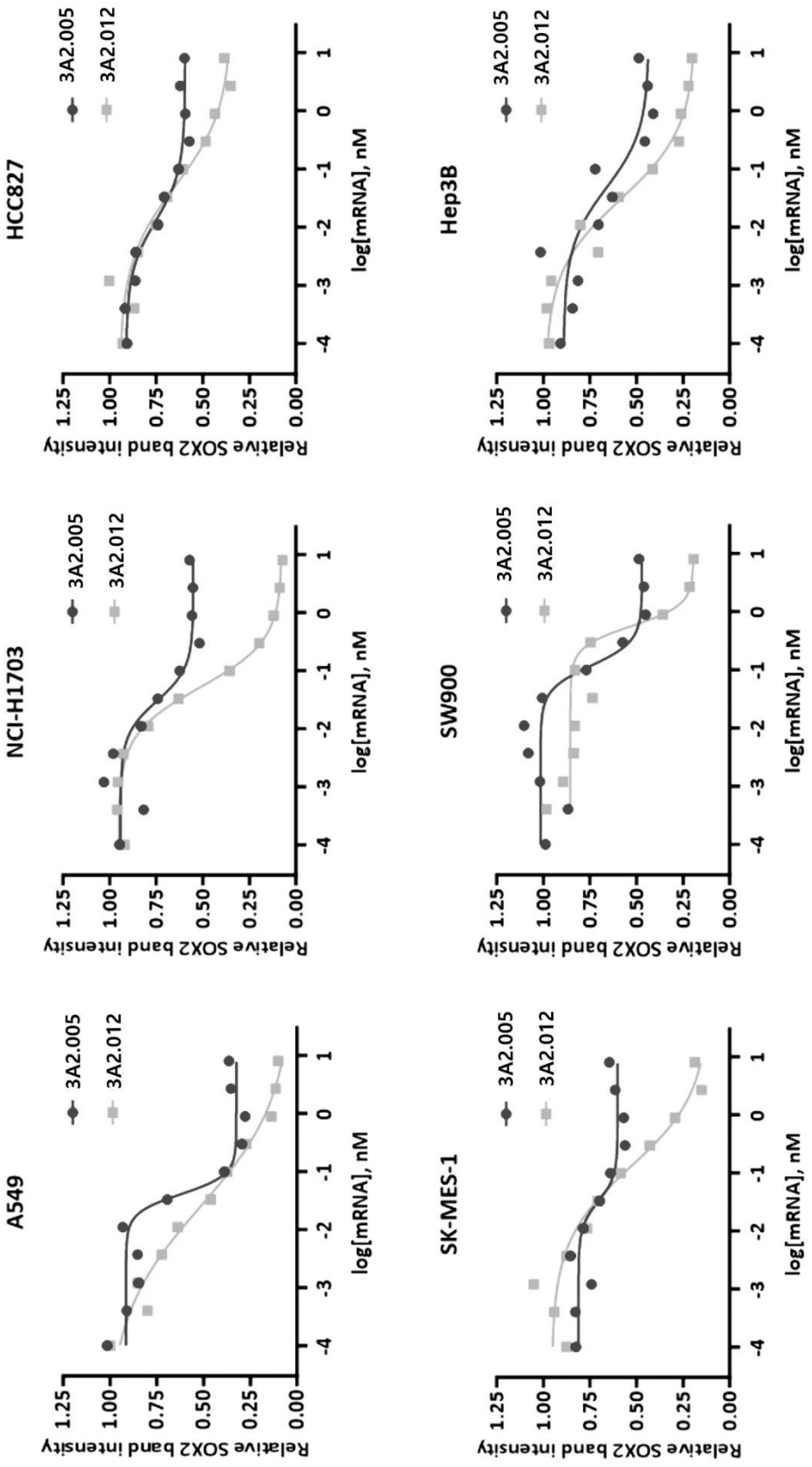
[FIG. 8b]


H69-Dox^R
Cell growth
Confluency (%)
80
60
40
20
0
Cell only
Doxorubicin
S14.010
S14.012
Doxorubicin (10 μM)
H69-Dox^R
Apoptosis
Green Object Count (Per Image)
2000
1500
1000
500
0
Cell only
Doxorubicin
S14.010
S14.012
Doxorubicin (10 μM)

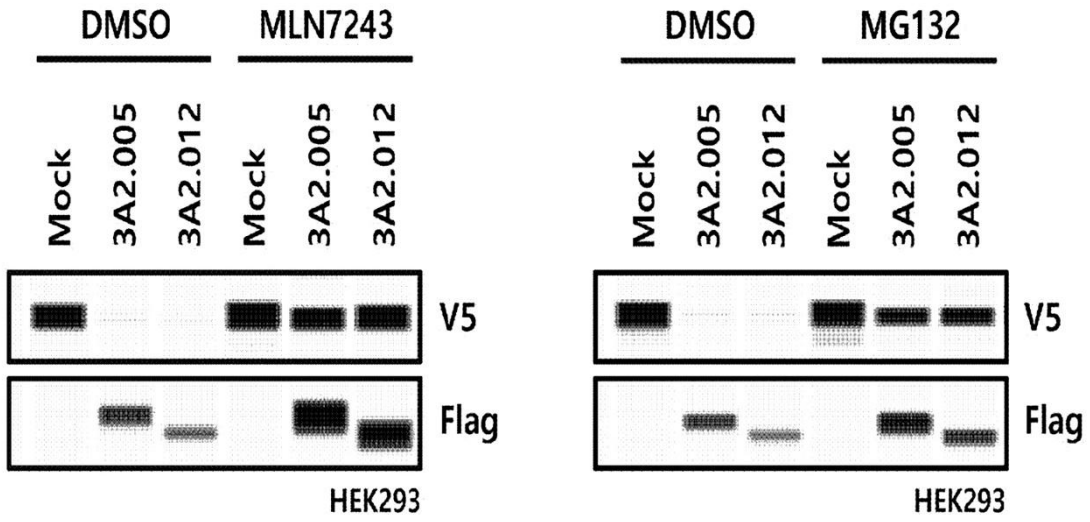
[FIG. 9]


a
Mock
3A2.004
3A2.005
3A2.006
3A2.007
3A2.010
3A2.011
3A2.012
3A2.018
3A2.019
3A2.020
V5
Flag
HEK293
SOX2 degradation
b
Relative band intensity
1.5
1.0
0.5
0.0
1.00
1.04
0.15 *
1.27
0.26 **
1.09
0.15 **
0.05 ***
0.75 **
1.03
0.82
Mock
3A2.004
3A2.005
3A2.006
3A2.007
3A2.010
3A2.011
3A2.012
3A2.018
3A2.019
3A2.020

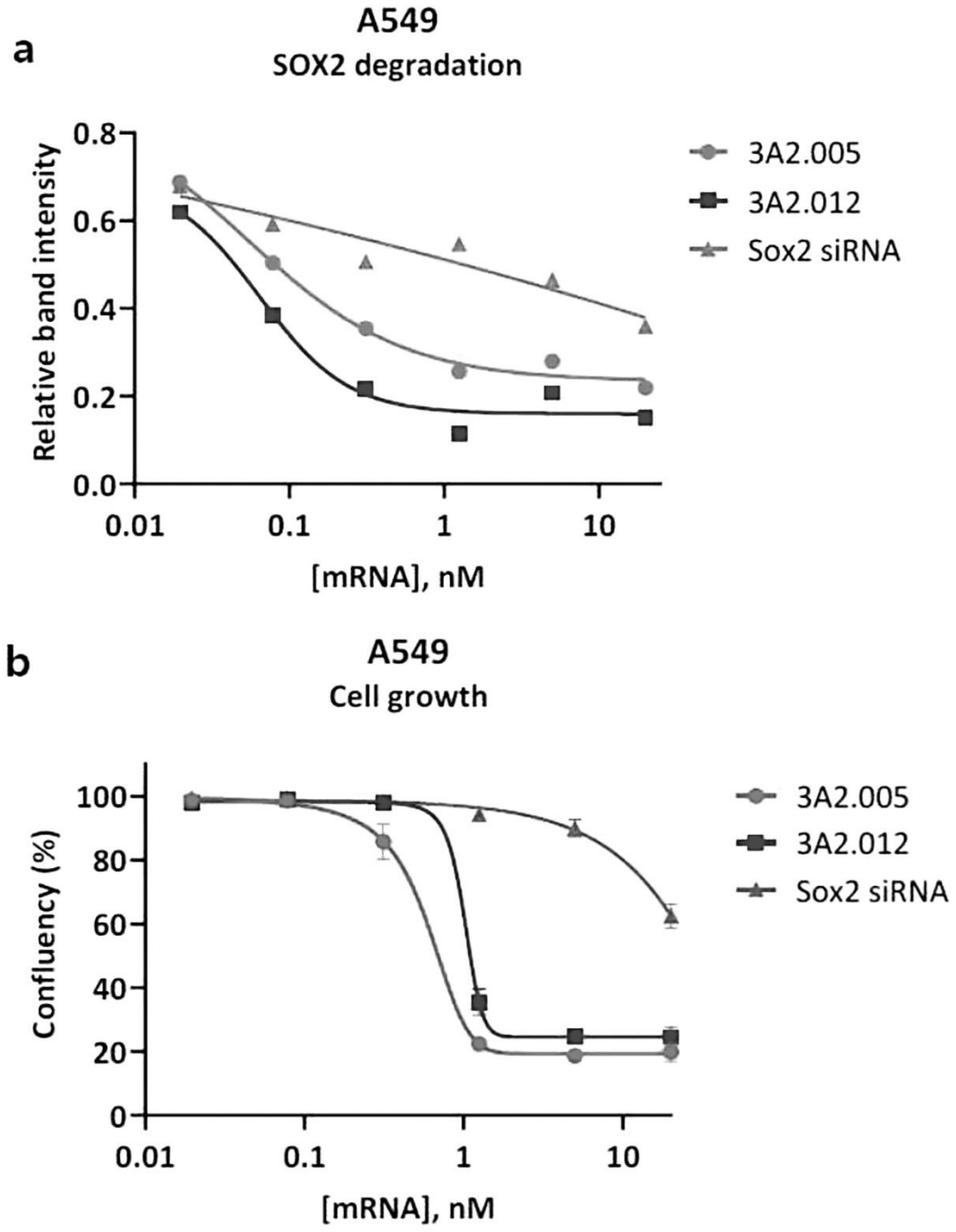
[FIG. 10]


A549
NCI-H1703
HCC827
SK-MES-1
SW900
Hep3B
3A2.005
3A2.012
Relative SOX2 band intensity
log[mRNA], nM
1.25
1.00
0.75
0.50
0.25
0.00
-4
-3
-2
-1
0
1

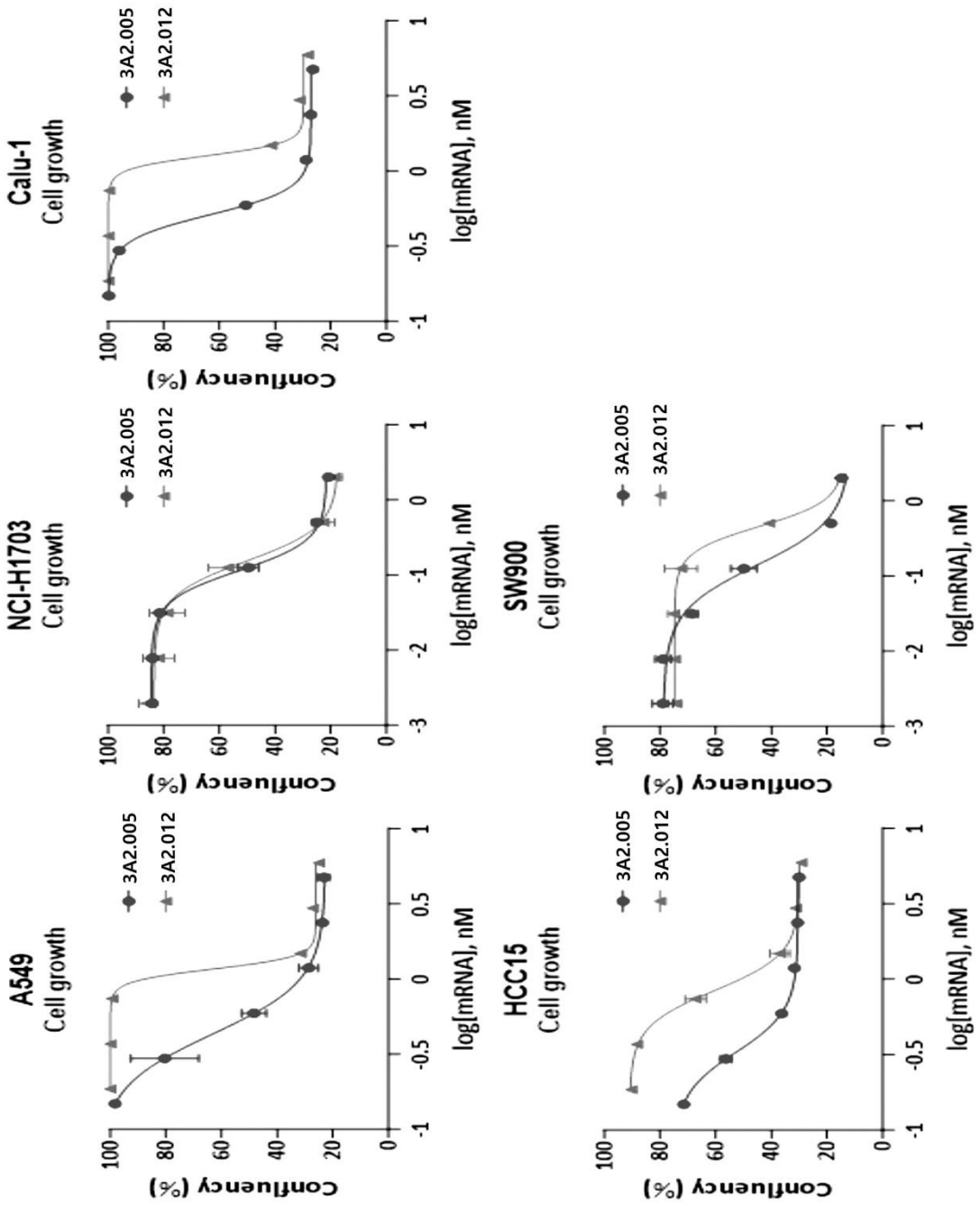
[FIG. 11]


DMSO
MLN7243
Mock
3A2.005
3A2.012
Mock
3A2.005
3A2.012
V5
Flag
HEK293
DMSO
MG132
Mock
3A2.005
3A2.012
Mock
3A2.005
3A2.012
V5
Flag
HEK293

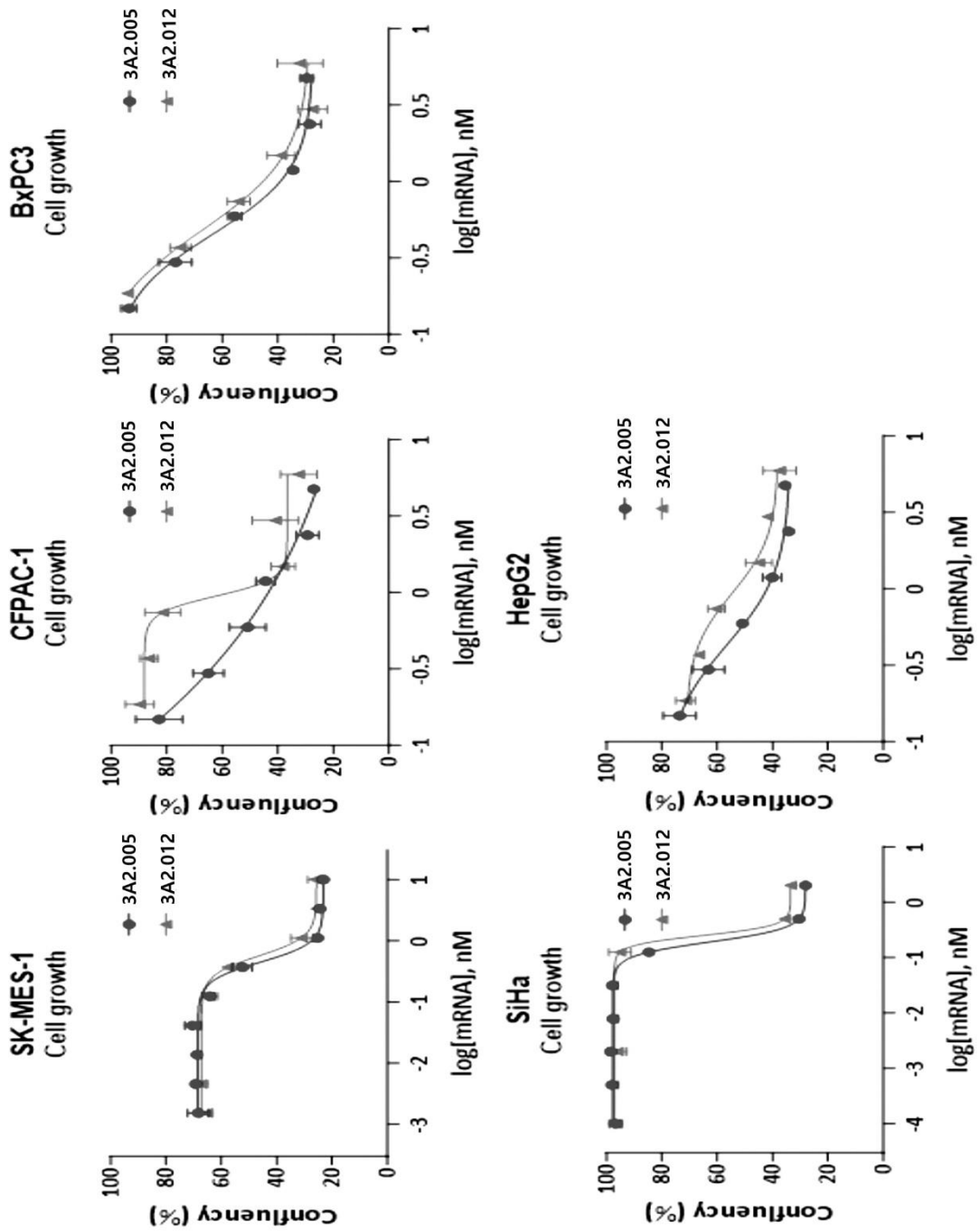
[FIG. 12]


a
A549
SOX2 degradation
Relative band intensity
0.8
0.6
0.4
0.2
0.0
0.01
0.1
1
10
[mRNA], nM
3A2.005
3A2.012
Sox2 siRNA
b
A549
Cell growth
Confluency (%)
100
80
60
40
20
0
0.01
0.1
1
10
[mRNA], nM
3A2.005
3A2.012
Sox2 siRNA

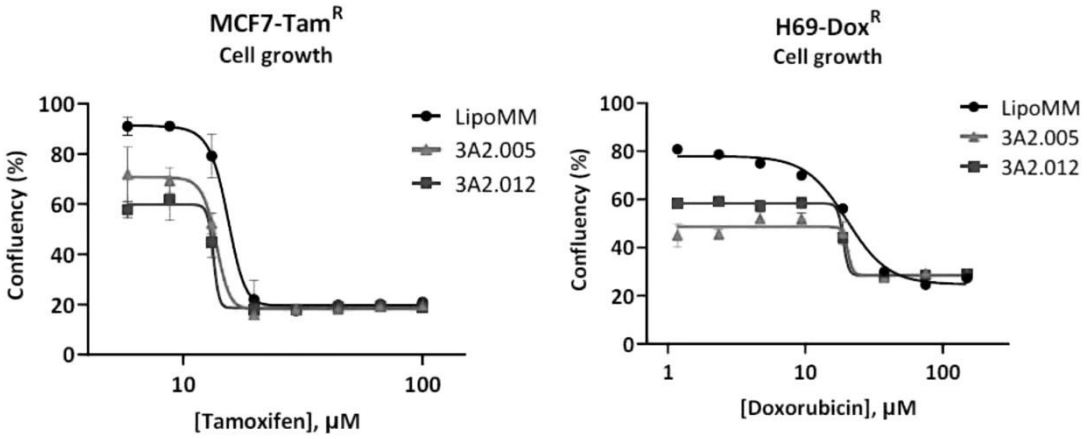
[FIG. 13a]


Calu-1
Cell growth
NCI-H1703
Cell growth
SW900
Cell growth
A549
Cell growth
HCC15
Cell growth
3A2.005
3A2.012
Confluency (%)
log[mRNA], nM

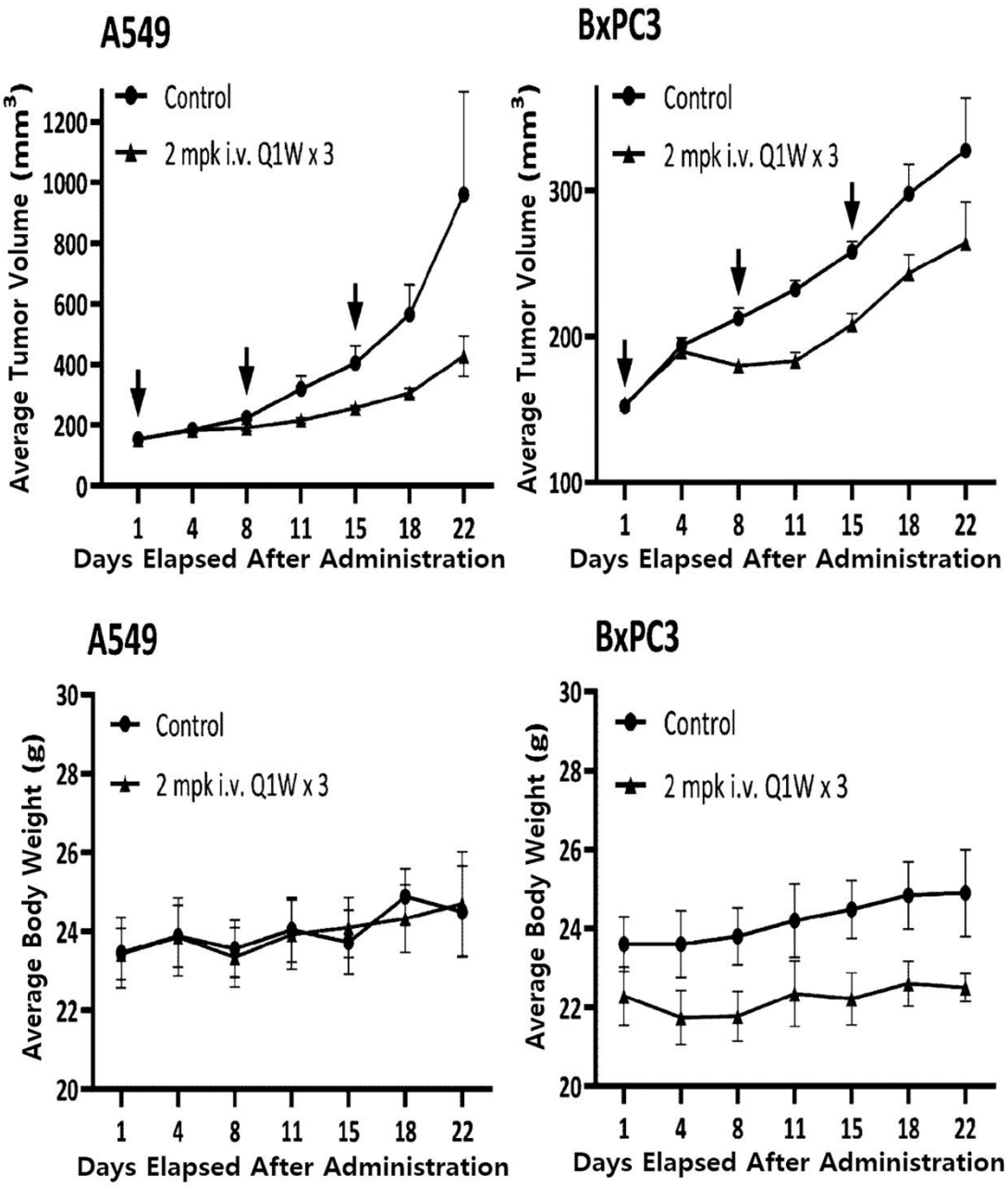
[FIG. 13b]


BxPC3
Cell growth
3A2.005
3A2.012
Confluency (%)
log[mRNA], nM
CFPAC-1
Cell growth
3A2.005
3A2.012
Confluency (%)
log[mRNA], nM
HepG2
Cell growth
3A2.005
3A2.012
Confluency (%)
log[mRNA], nM
SK-MES-1
Cell growth
3A2.005
3A2.012
Confluency (%)
log[mRNA], nM
SiHa
Cell growth
3A2.005
3A2.012
Confluency (%)
log[mRNA], nM

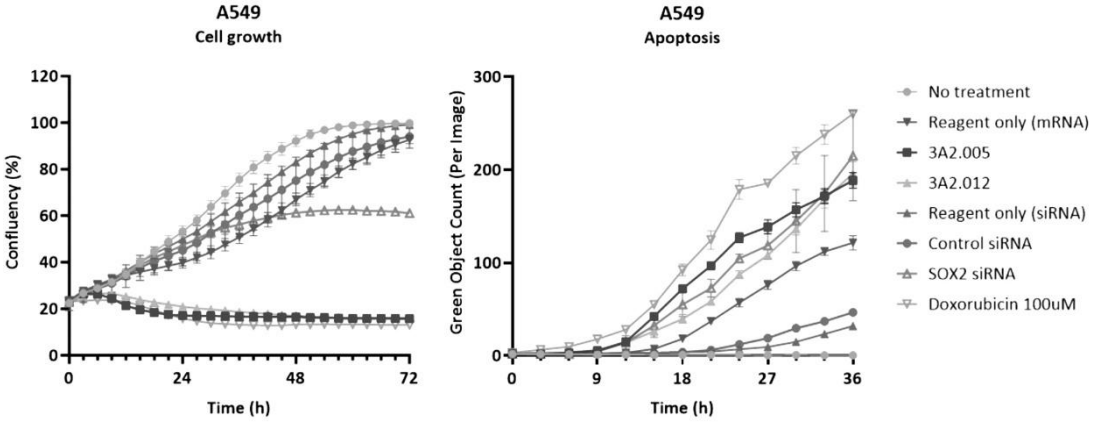
[FIG. 14]


MCF7-Tam^R
Cell growth
Confluency (%)
100
80
60
40
20
0
10
100
[Tamoxifen], μM
LipoMM
3A2.005
3A2.012
H69-Dox^R
Cell growth
Confluency (%)
100
80
60
40
20
0
1
10
100
[Doxorubicin], μM
LipoMM
3A2.005
3A2.012

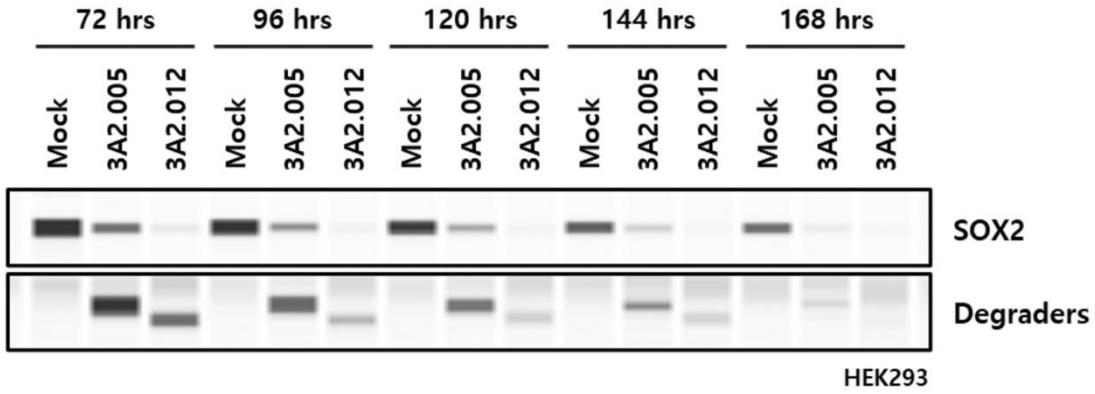
[FIG. 15]


A549
Control
2 mpk i.v. Q1W x 3
Average Tumor Volume (mm3)
0
200
400
600
800
1000
1200
1 4 8 11 15 18 22
Days Elapsed After Administration
BxPC3
Control
2 mpk i.v. Q1W x 3
Average Tumor Volume (mm3)
100
200
300
1 4 8 11 15 18 22
Days Elapsed After Administration
A549
Control
2 mpk i.v. Q1W x 3
Average Body Weight (g)
20
22
24
26
28
30
1 4 8 11 15 18 22
Days Elapsed After Administration
BxPC3
Control
2 mpk i.v. Q1W x 3
Average Body Weight (g)
20
22
24
26
28
30
1 4 8 11 15 18 22
Days Elapsed After Administration

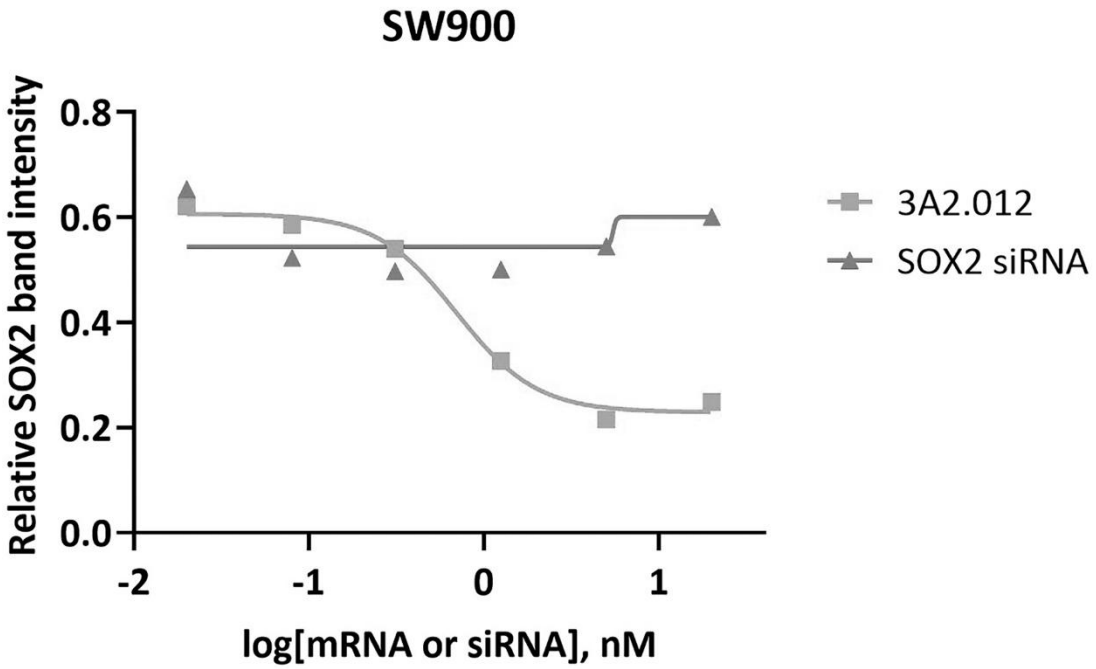
[FIG. 16]


A549
Cell growth
Confluency (%)
120
100
80
60
40
20
0
0
24
48
72
Time (h)
A549
Apoptosis
Green Object Count (Per Image)
300
200
100
0
0
9
18
27
36
Time (h)
No treatment
Reagent only (mRNA)
3A2.005
3A2.012
Reagent only (siRNA)
Control siRNA
SOX2 siRNA
Doxorubicin 100uM

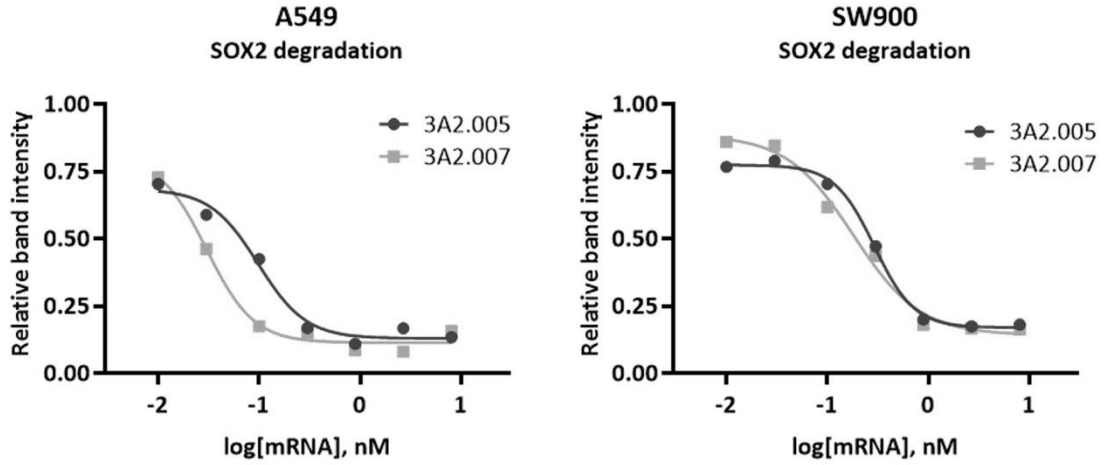
[FIG. 17]


72 hrs
96 hrs
120 hrs
144 hrs
168 hrs
Mock
3A2.005
3A2.012
SOX2
Degraders
HEK293

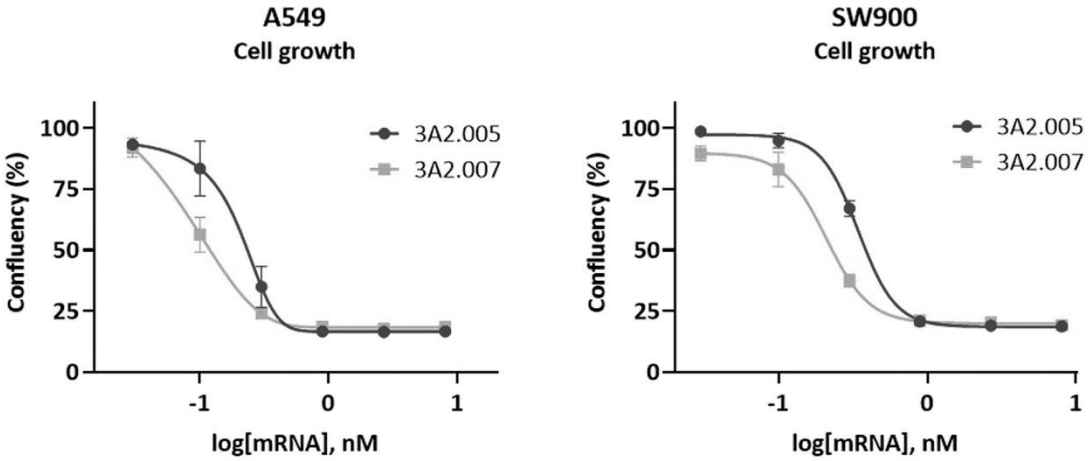
[FIG. 18]


SW900
Relative SOX2 band intensity
0.8
0.6
0.4
0.2
0.0
-2
-1
0
1
log[mRNA or siRNA], nM
3A2.012
SOX2 siRNA

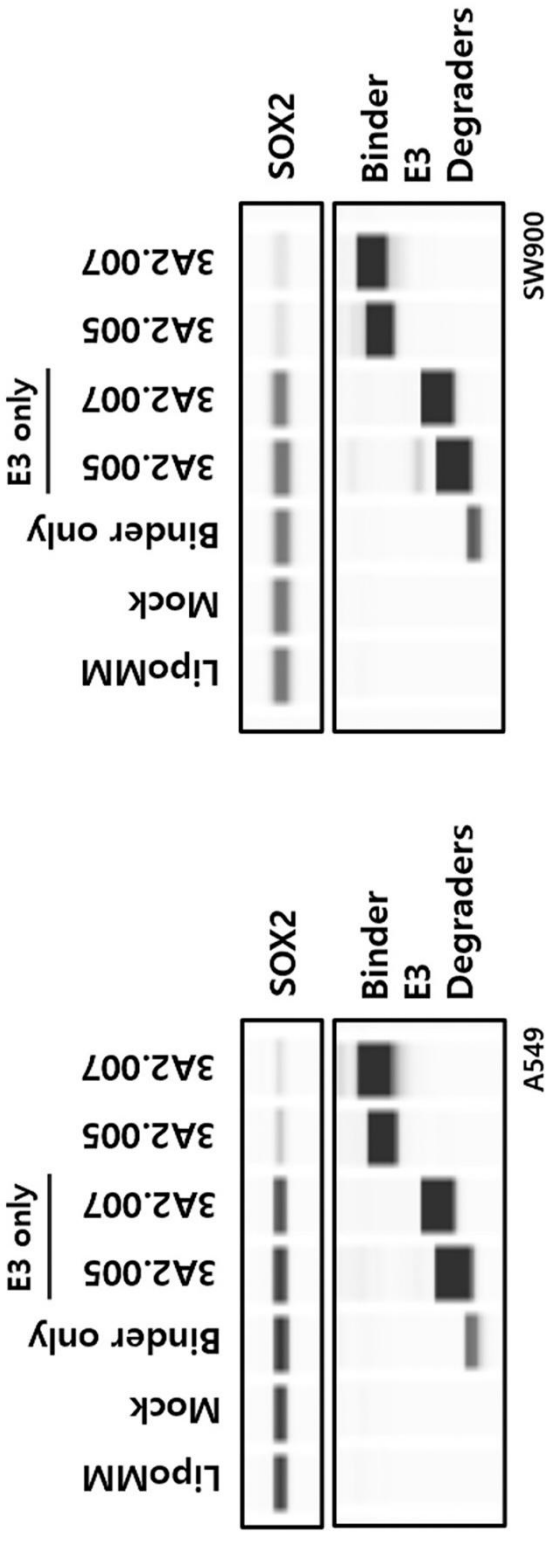
[FIG. 19]


A549
SOX2 degradation
Relative band intensity
1.00
0.75
0.50
0.25
0.00
-2
-1
0
1
log[mRNA], nM
3A2.005
3A2.007
SW900
SOX2 degradation
Relative band intensity
1.00
0.75
0.50
0.25
0.00
-2
-1
0
1
log[mRNA], nM
3A2.005
3A2.007

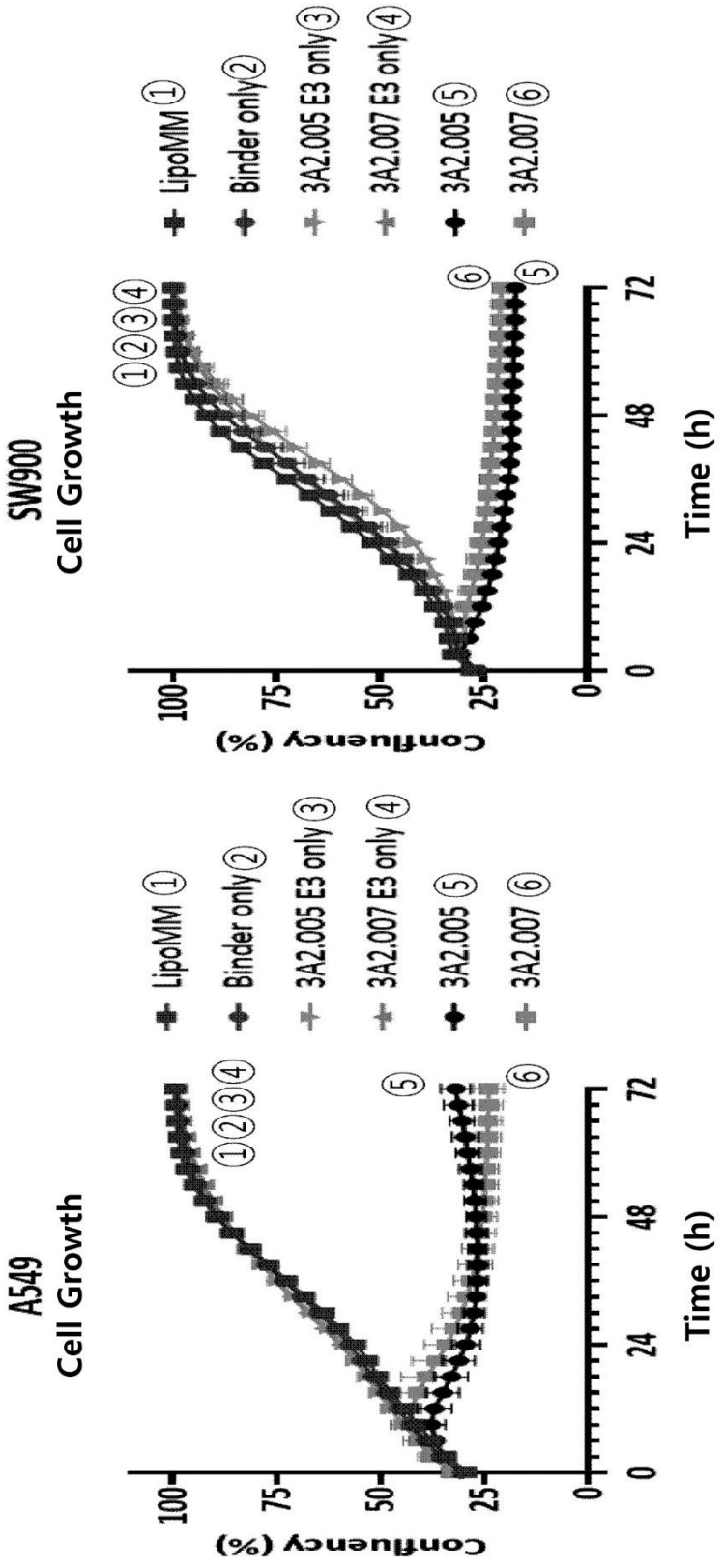
[FIG. 20]


A549
Cell growth
Confluency (%)
100
75
50
25
0
-1
0
1
log[mRNA], nM
3A2.005
3A2.007
SW900
Cell growth
Confluency (%)
100
75
50
25
0
-1
0
1
log[mRNA], nM
3A2.005
3A2.007

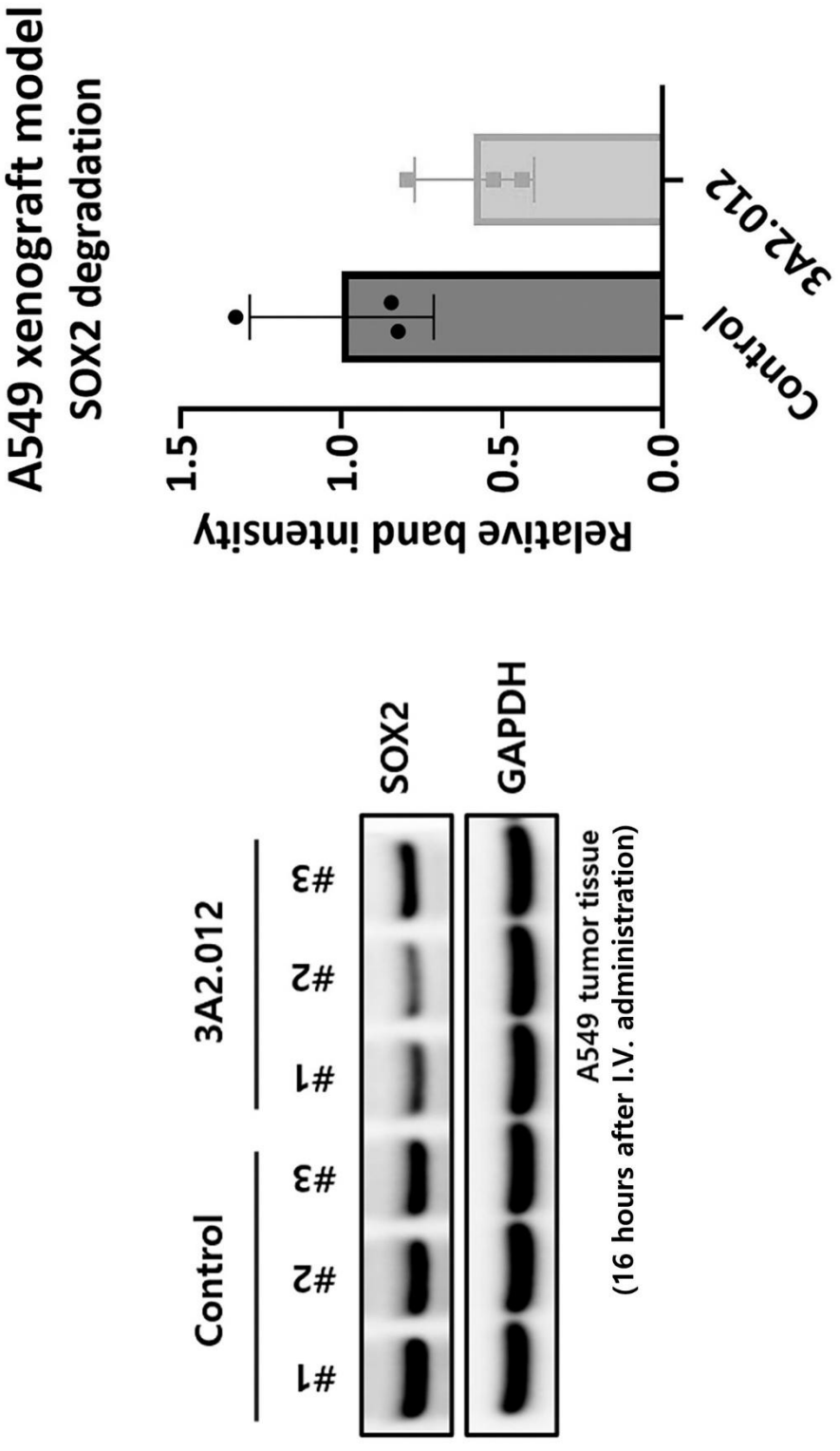
[FIG. 21a]


SW900
A549
SOX2
Binder
E3
Degraders
LipoMM
Mock
Binder only
E3 only
3A2.005
3A2.007
3A2.005
3A2.007

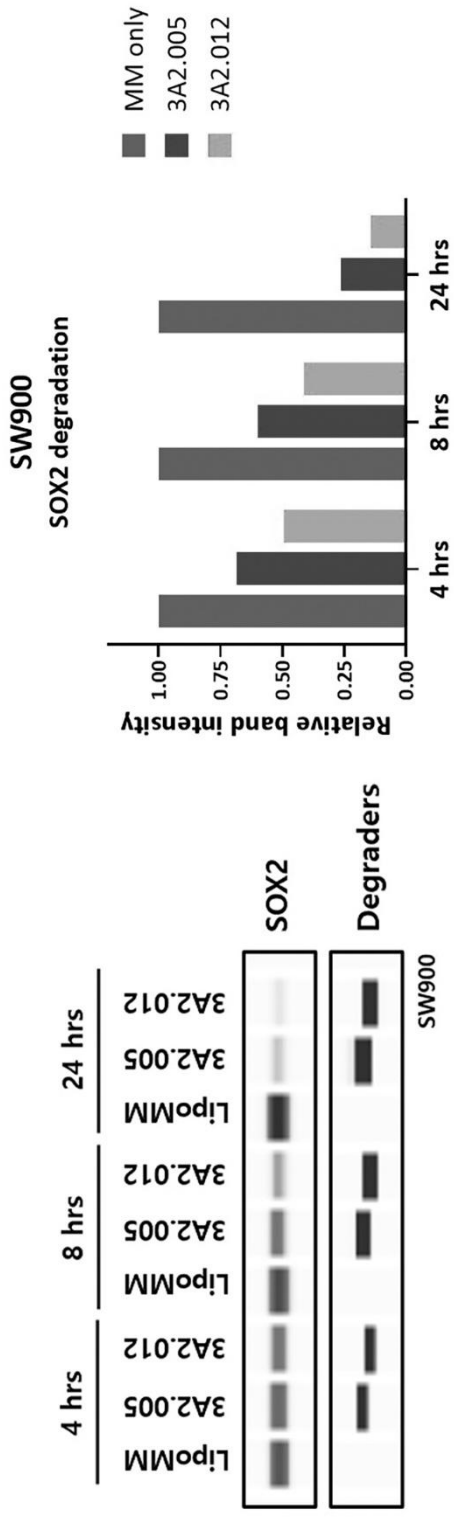
[FIG. 21b]


SW900
Cell Growth
A549
Cell Growth
Confluency (%)
Time (h)
LipoMM ①
Binder only ②
3A2.005 E3 only ③
3A2.007 E3 only ④
3A2.005 ⑤
3A2.007 ⑥
①②③④
⑤
⑥
0
25
50
75
100
0
24
48
72

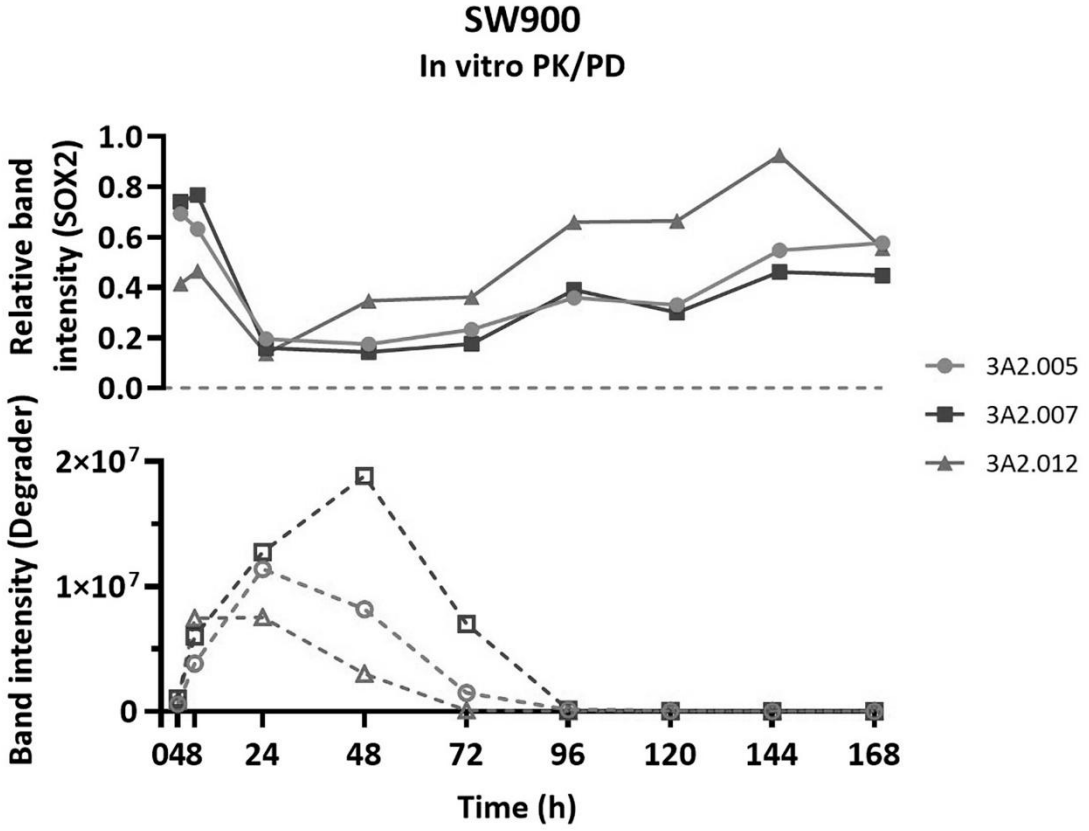
[FIG. 22]


A549 xenograft model
SOX2 degradation
Relative band intensity
1.5
1.0
0.5
0.0
Control
3A2.012
SOX2
GAPDH
Control
3A2.012
#1
#2
#3
#1
#2
#3
A549 tumor tissue
(16 hours after I.V. administration)

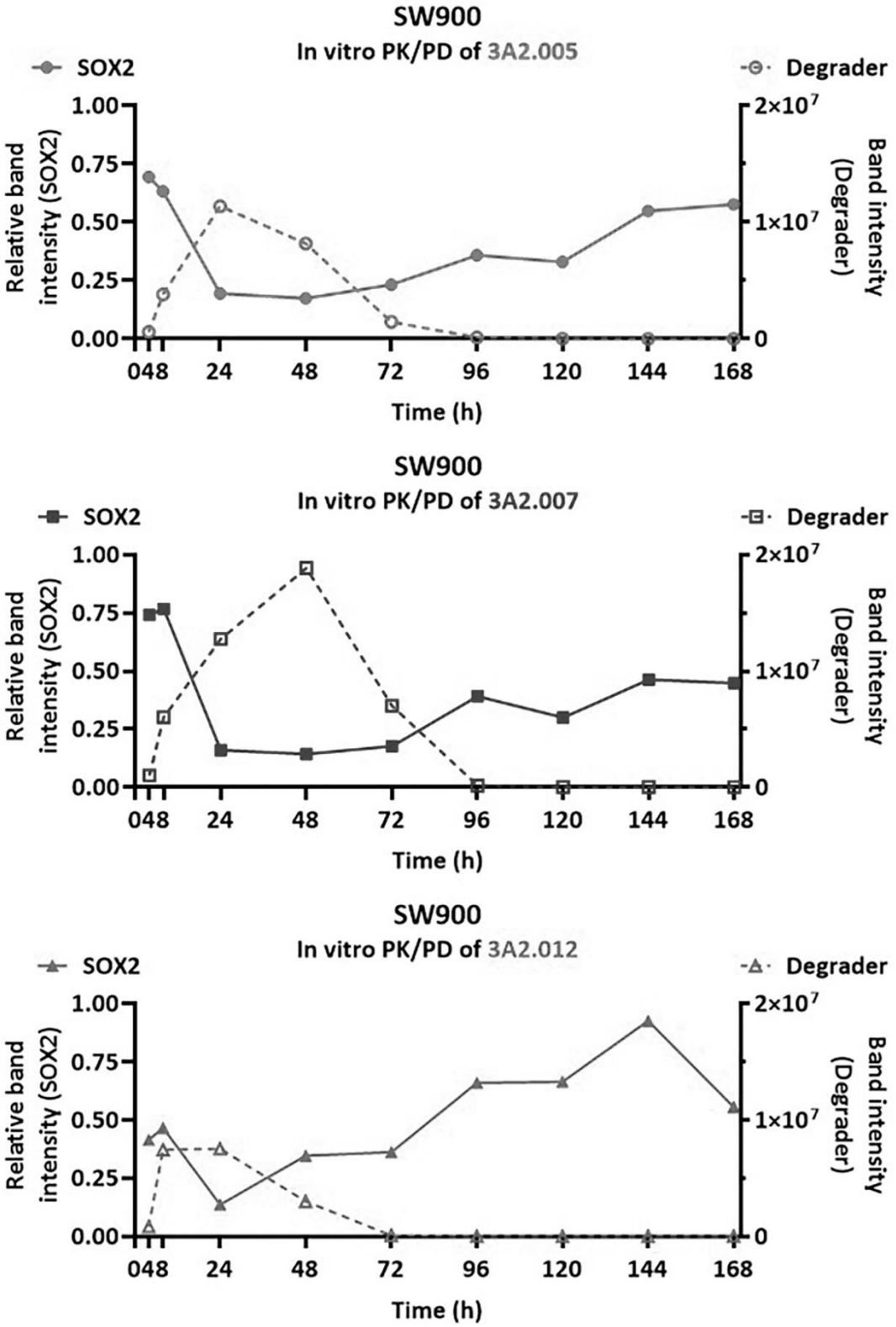
[FIG. 23]


SW900
SOX2 degradation
MM only
3A2.005
3A2.012
Relative band intensity
0.00
0.25
0.50
0.75
1.00
4 hrs
8 hrs
24 hrs
SOX2
Degraders
SW900
LipoMM
3A2.005
3A2.012
LipoMM
3A2.005
3A2.012
LipoMM
3A2.005
3A2.012

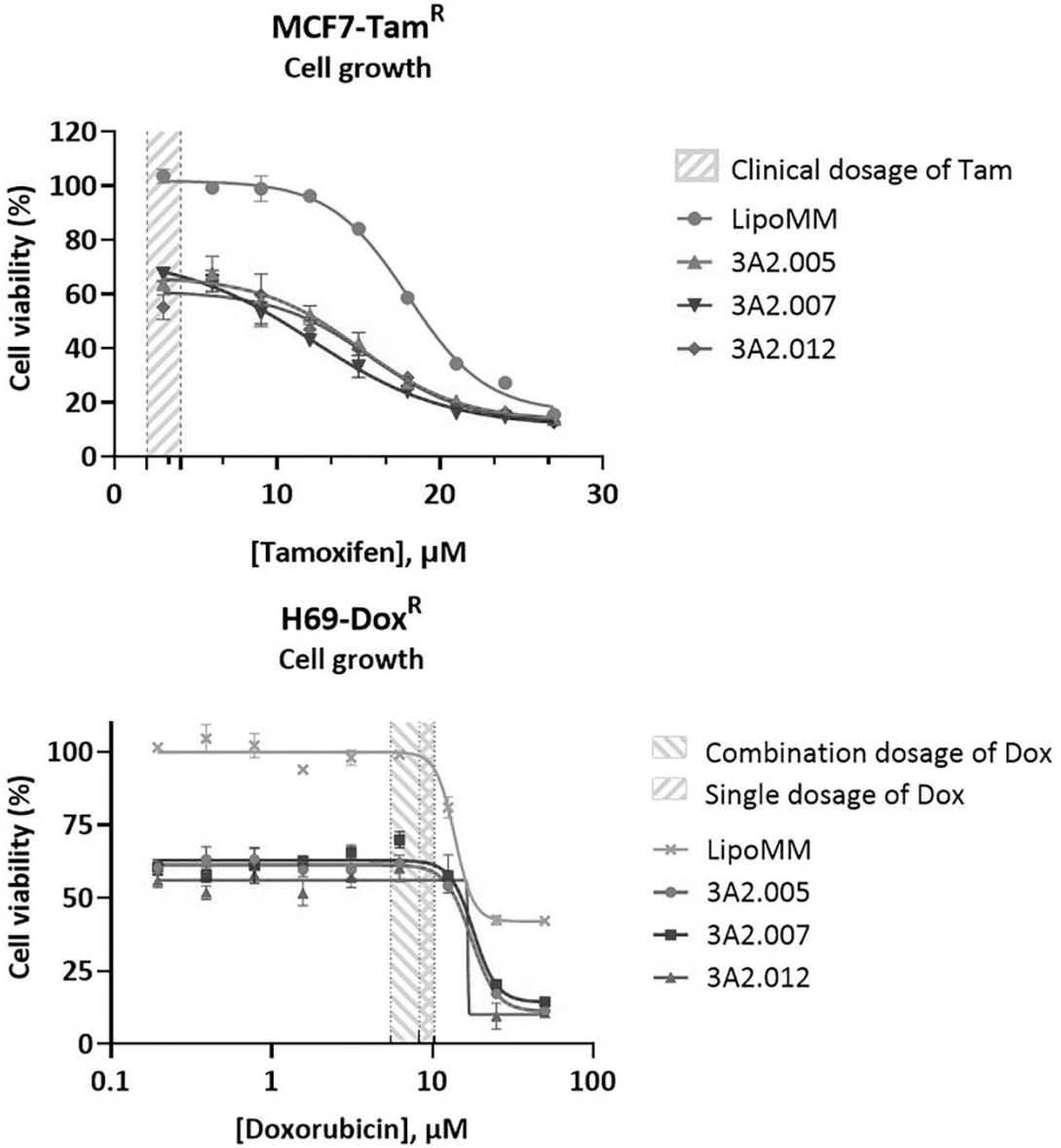
[FIG. 24a]


SW900
In vitro PK/PD
Relative band intensity (SOX2)
1.0
0.8
0.6
0.4
0.2
0.0
Band intensity (Degrader)
2×10^7
1×10^7
0
048
24
48
72
96
120
144
168
Time (h)
3A2.005
3A2.007
3A2.012

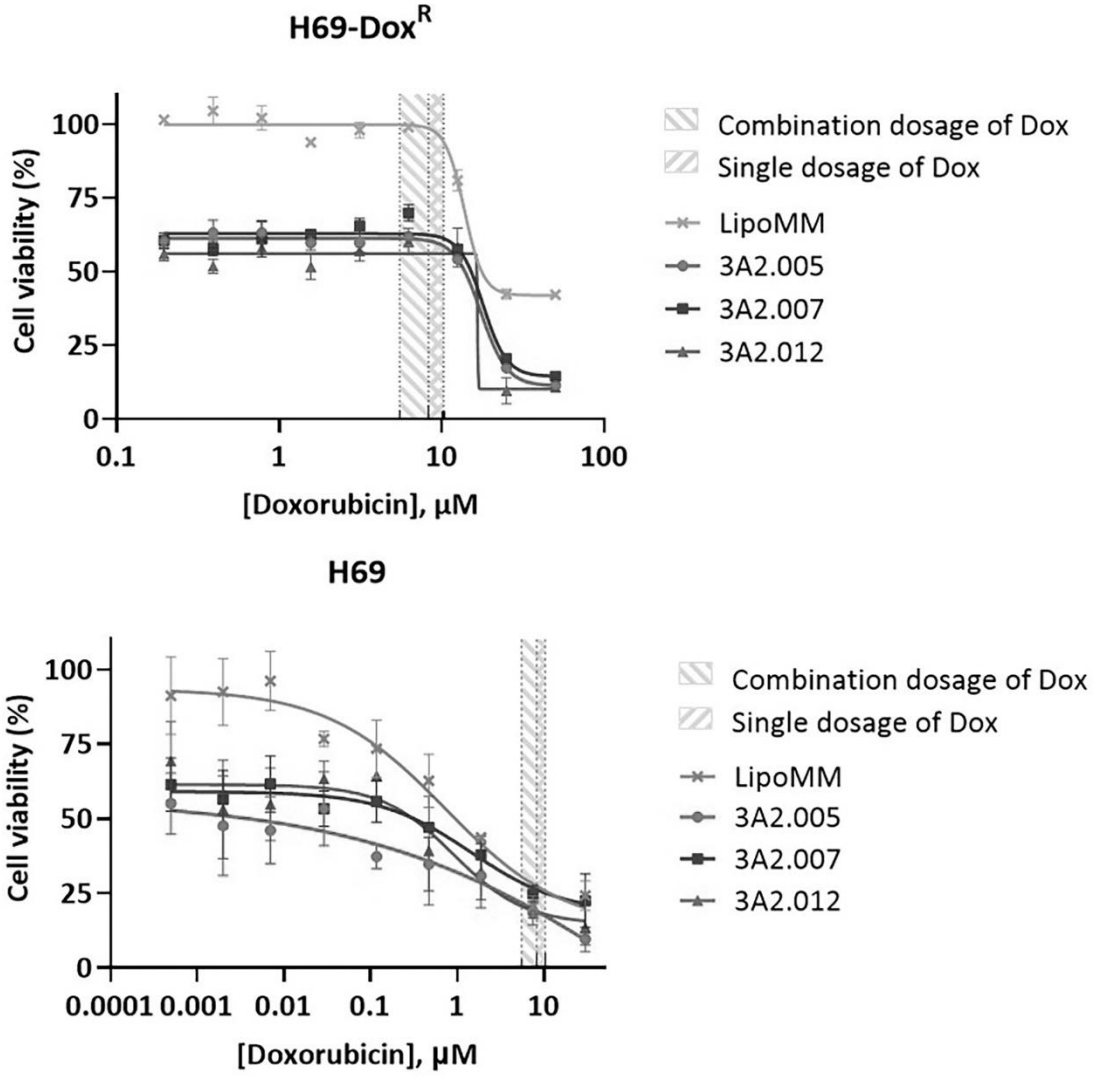
[FIG. 24b]


SW900
In vitro PK/PD of 3A2.005
SOX2
Degrader
Relative band intensity (SOX2)
Band intensity (Degrader)
1.00
0.75
0.50
0.25
0.00
2×10^7
1×10^7
0
048
24
48
72
96
120
144
168
Time (h)
SW900
In vitro PK/PD of 3A2.007
SOX2
Degrader
Relative band intensity (SOX2)
Band intensity (Degrader)
Time (h)
SW900
In vitro PK/PD of 3A2.012
SOX2
Degrader
Relative band intensity (SOX2)
Band intensity (Degrader)
Time (h)

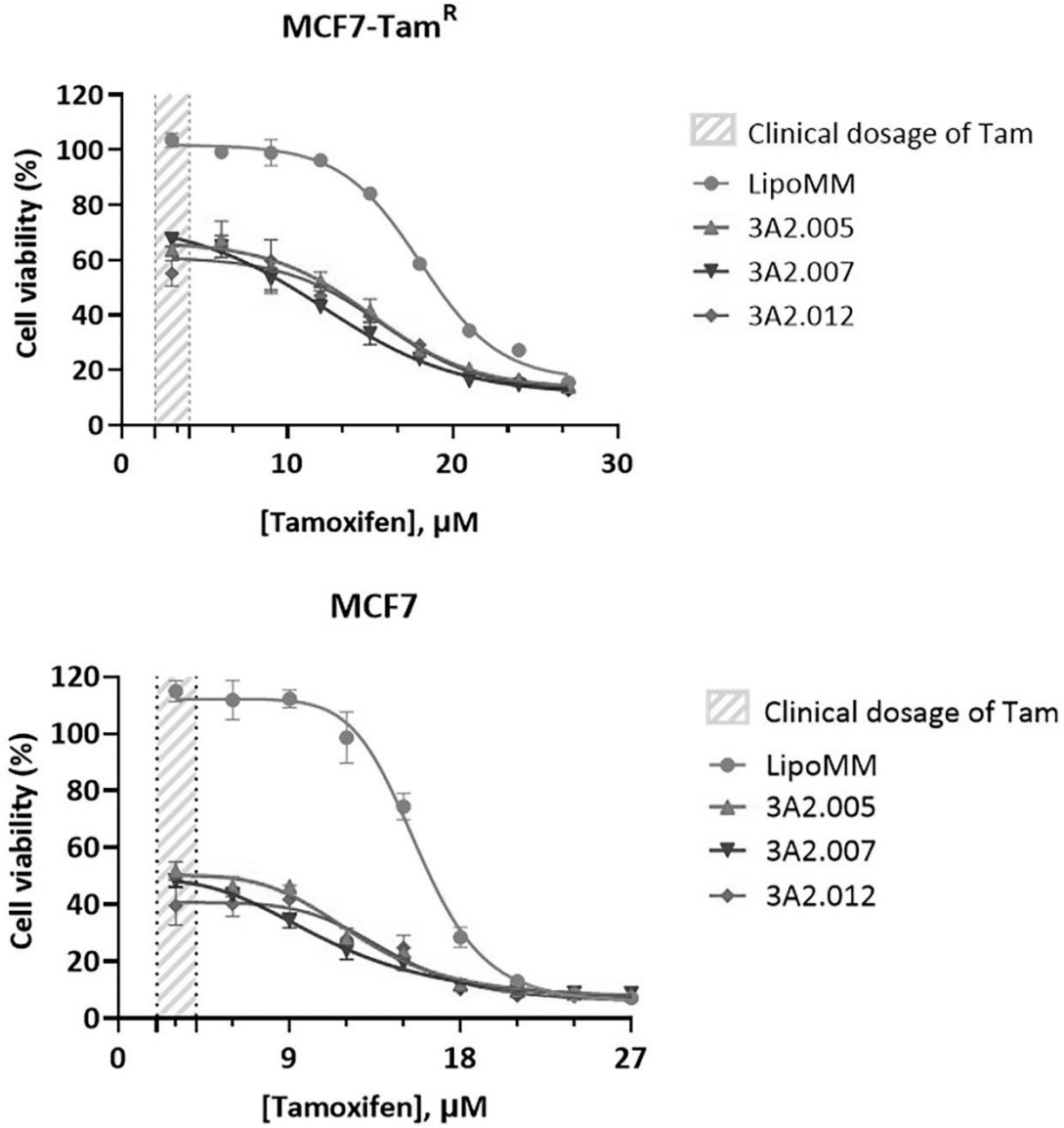
[FIG. 25]


MCF7-Tam^R
Cell growth
Cell viability (%)
120
100
80
60
40
20
0
0
10
20
30
[Tamoxifen], μM
Clinical dosage of Tam
LipoMM
3A2.005
3A2.007
3A2.012
H69-Dox^R
Cell growth
Cell viability (%)
100
75
50
25
0
0.1
1
10
100
[Doxorubicin], μM
Combination dosage of Dox
Single dosage of Dox
LipoMM
3A2.005
3A2.007
3A2.012

[FIG. 26]


H69-Dox^R
Cell viability (%)
100
75
50
25
0
0.1
1
10
100
[Doxorubicin], μM
Combination dosage of Dox
Single dosage of Dox
LipoMM
3A2.005
3A2.007
3A2.012
H69
Cell viability (%)
100
75
50
25
0
0.0001
0.001
0.01
0.1
1
10
[Doxorubicin], μM
Combination dosage of Dox
Single dosage of Dox
LipoMM
3A2.005
3A2.007
3A2.012

[FIG. 27]


MCF7-Tam^R
Cell viability (%)
120
100
80
60
40
20
0
0
10
20
30
[Tamoxifen], μM
Clinical dosage of Tam
LipoMM
3A2.005
3A2.007
3A2.012
MCF7
Cell viability (%)
120
100
80
60
40
20
0
0
9
18
27
[Tamoxifen], μM
Clinical dosage of Tam
LipoMM
3A2.005
3A2.007
3A2.012