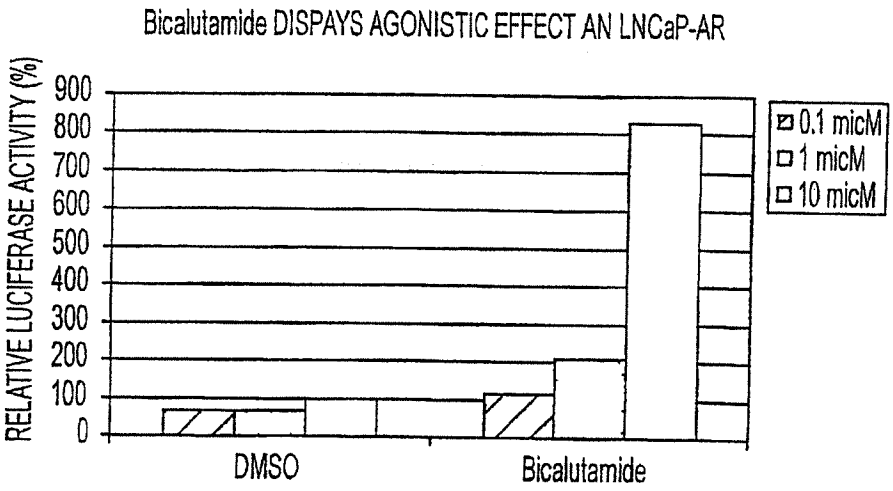

Bicalutamide DISPAYS AGONISTIC EFFECT AN LNCaP-AR
RELATIVE LUCIFERASE ACTIVITY (%)
900
800
700
600
500
400
300
200
100
0
DMSO
Bicalutamide
0.1 micM
1 micM
10 micM

FIG. 1

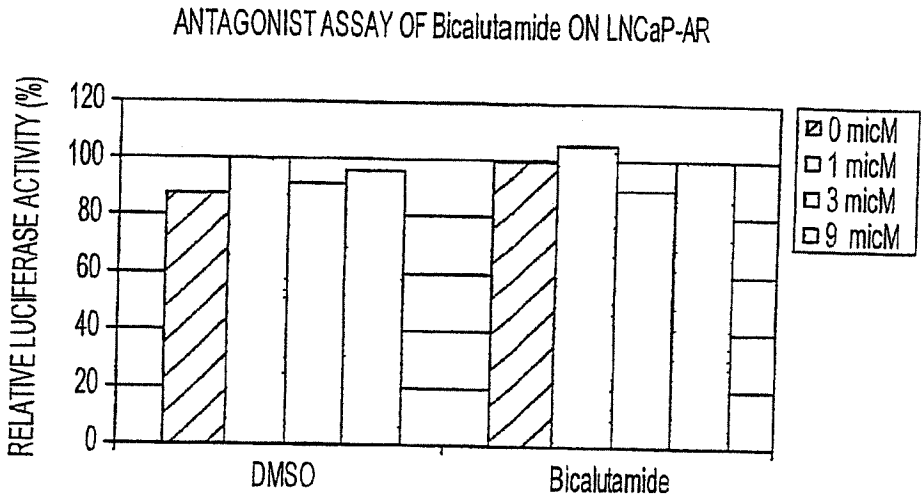

ANTAGONIST ASSAY OF Bicalutamide ON LNCaP-AR
RELATIVE LUCIFERASE ACTIVITY (%)
120
100
80
60
40
20
0
DMSO
Bicalutamide
0 micM
1 micM
3 micM
9 micM

FIG. 2

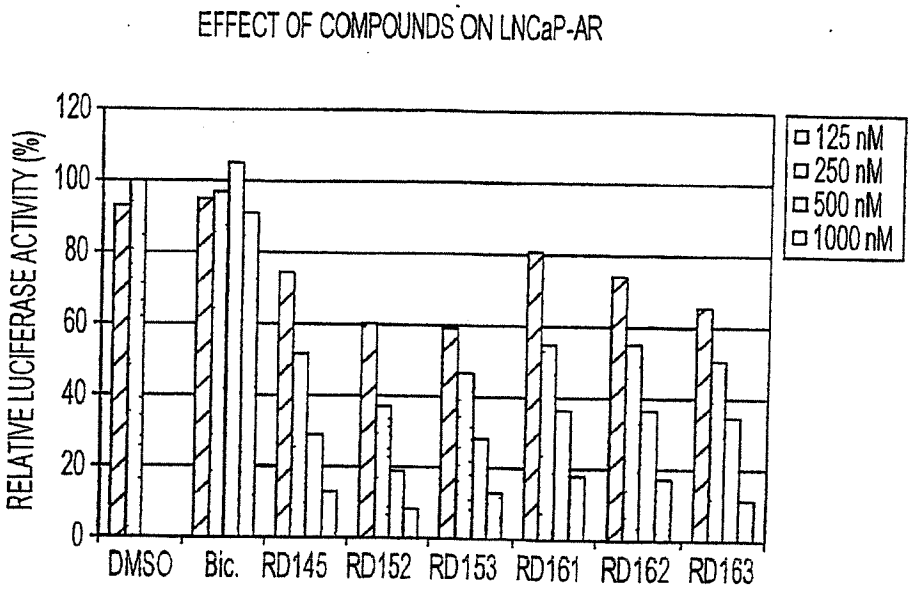

EFFECT OF COMPOUNDS ON LNCaP-AR
RELATIVE LUCIFERASE ACTIVITY (%)
120
100
80
60
40
20
0
DMSO
Bic.
RD145
RD152
RD153
RD161
RD162
RD163
125 nM
250 nM
500 nM
1000 nM

FIG. 3

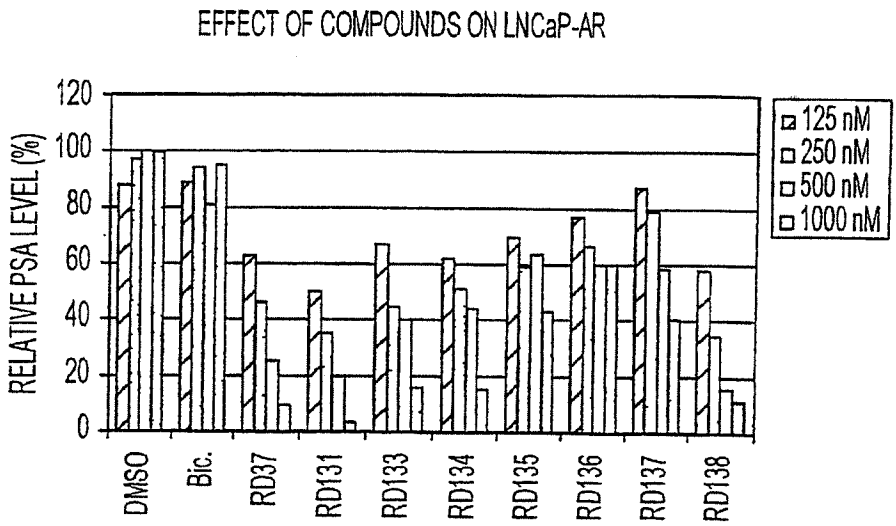

EFFECT OF COMPOUNDS ON LNCaP-AR
RELATIVE PSA LEVEL (%)
120
100
80
60
40
20
0
DMSO
Bic.
RD37
RD131
RD133
RD134
RD135
RD136
RD137
RD138
125 nM
250 nM
500 nM
1000 nM

FIG. 4

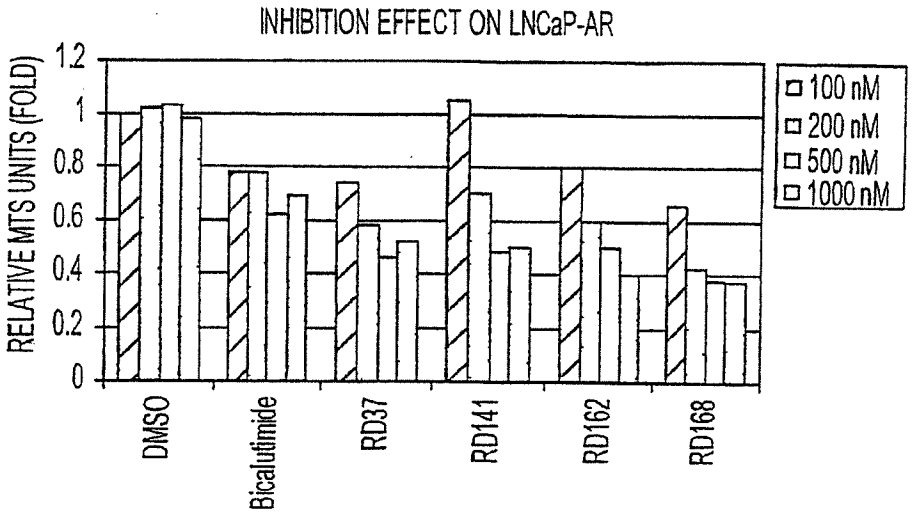

INHIBITION EFFECT ON LNCaP-AR
RELATIVE MTS UNITS (FOLD)
1.2
1
0.8
0.6
0.4
0.2
0
100 nM
200 nM
500 nM
1000 nM
DMSO
Bicalutimide
RD37
RD141
RD162
RD168

FIG. 5

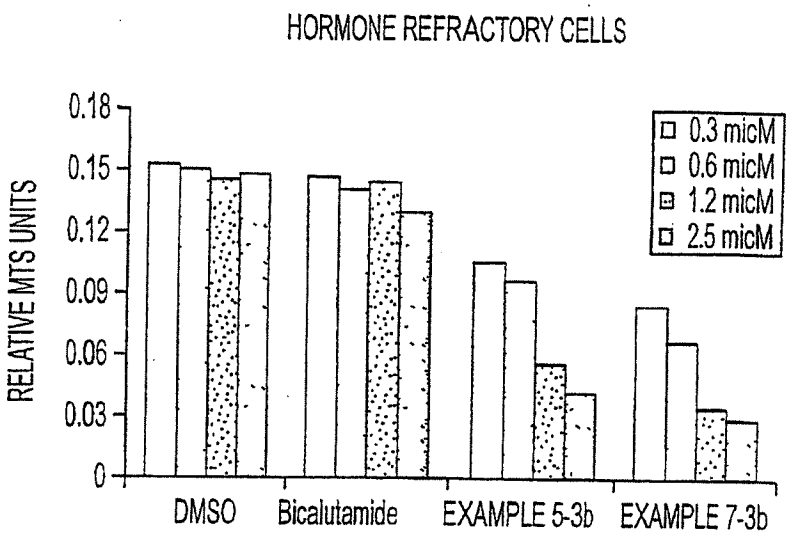

HORMONE REFRACTORY CELLS
RELATIVE MTS UNITS
0.18
0.15
0.12
0.09
0.06
0.03
0
0.3 micM
0.6 micM
1.2 micM
2.5 micM
DMSO
Bicalutamide
EXAMPLE 5-3b
EXAMPLE 7-3b

FIG. 6

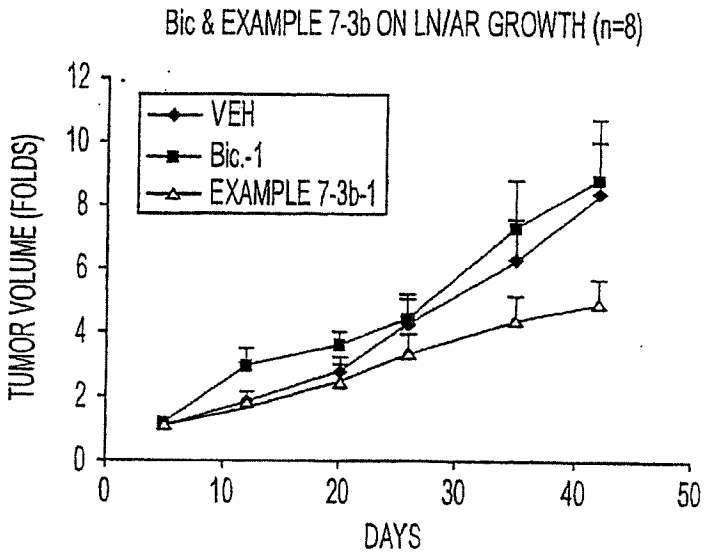

Bic & EXAMPLE 7-3b ON LN/AR GROWTH (n=8)
TUMOR VOLUME (FOLDS)
DAYS
VEH
Bic.-1
EXAMPLE 7-3b-1
0
2
4
6
8
10
12
0
10
20
30
40
50

FIG. 7A

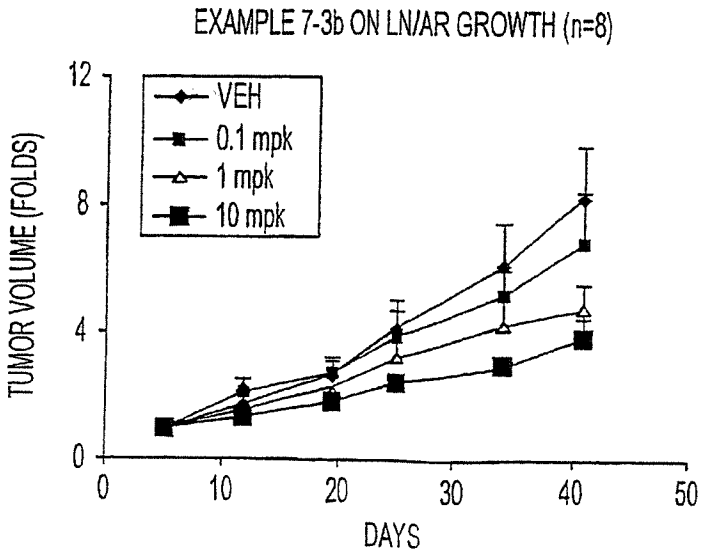

EXAMPLE 7-3b ON LN/AR GROWTH (n=8)
TUMOR VOLUME (FOLDS)
DAYS
VEH
0.1 mpk
1 mpk
10 mpk
0
4
8
12
0
10
20
30
40
50

FIG. 7B

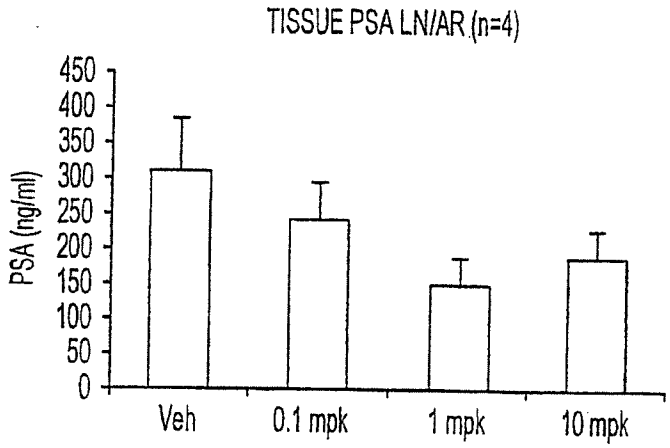

TISSUE PSA LN/AR (n=4)
PSA (ng/ml)
450
400
350
300
250
200
150
100
50
0
Veh
0.1 mpk
1 mpk
10 mpk

FIG. 8

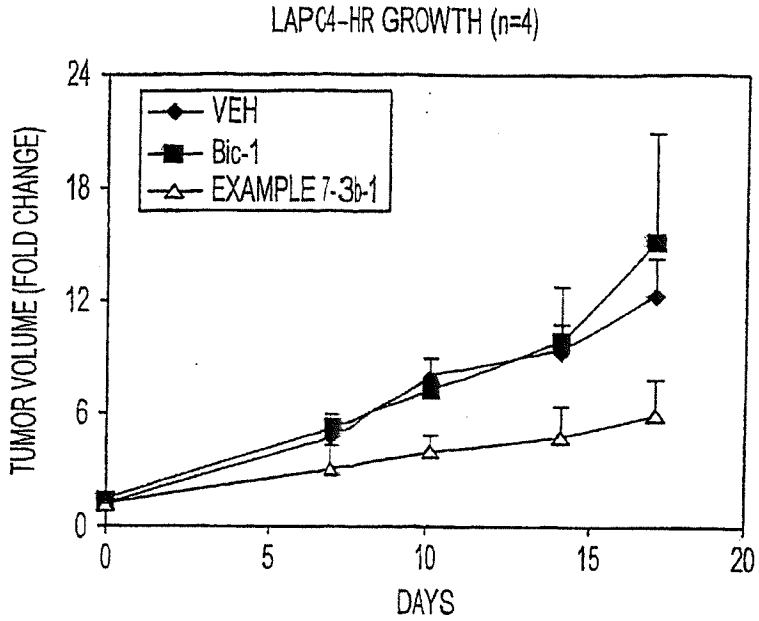

LAPC4-HR GROWTH (n=4)
TUMOR VOLUME (FOLD CHANGE)
24
18
12
6
0
VEH
Bic-1
EXAMPLE 7-3b-1
0
5
10
15
20
DAYS

FIG. 9A

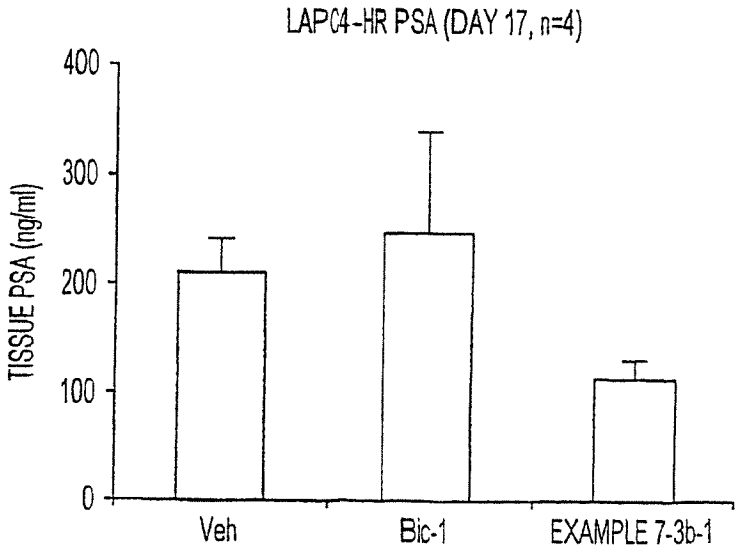

LAPC4-HR PSA (DAY 17, n=4)
TISSUE PSA (ng/ml)
400
300
200
100
0
Veh
Bic-1
EXAMPLE 7-3b-1

FIG. 9B

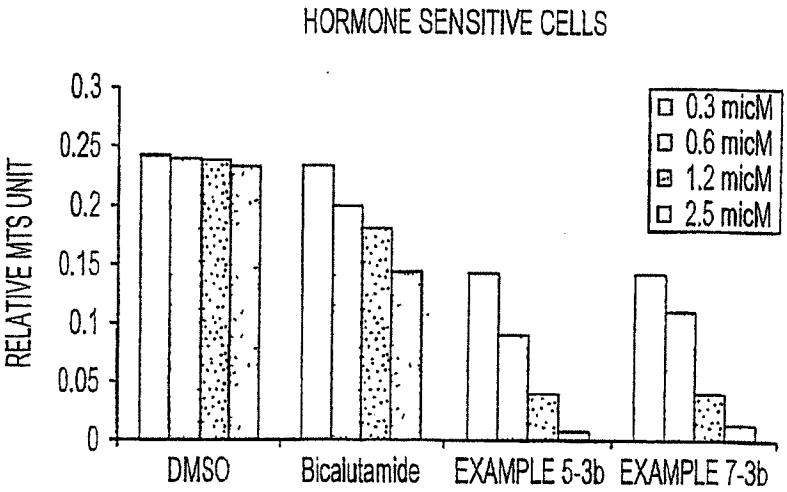

HORMONE SENSITIVE CELLS
RELATIVE MTS UNIT
0.3
0.25
0.2
0.15
0.1
0.05
0
0.3 micM
0.6 micM
1.2 micM
2.5 micM
DMSO
Bicalutamide
EXAMPLE 5-3b
EXAMPLE 7-3b

FIG. 10

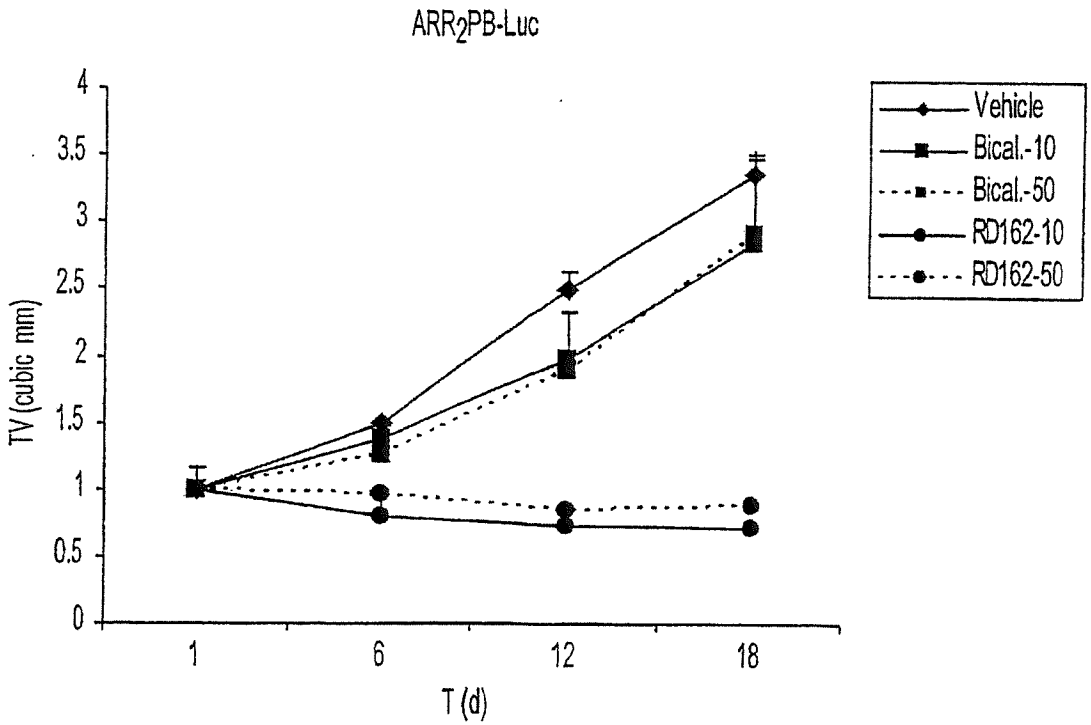

ARR2PB-Luc
TV (cubic mm)
4
3.5
3
2.5
2
1.5
1
0.5
0
1
6
12
18
T (d)
Vehicle
Bical.-10
Bical.-50
RD162-10
RD162-50

FIG. 11

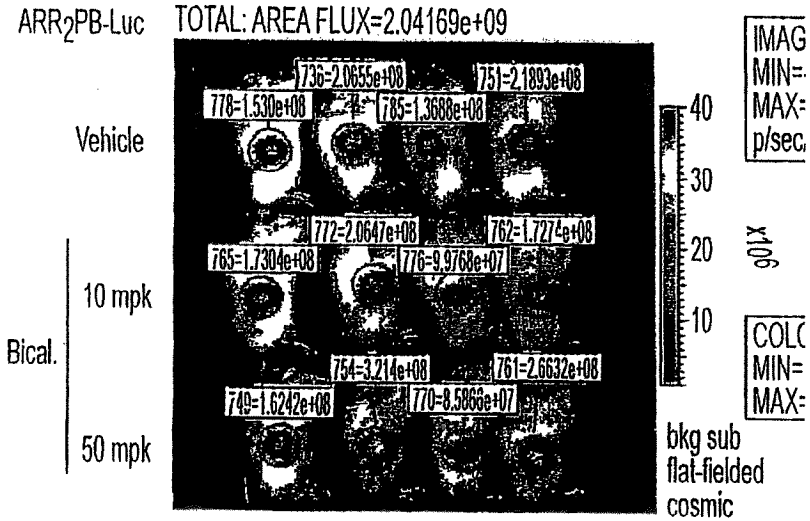


FIG. 12A

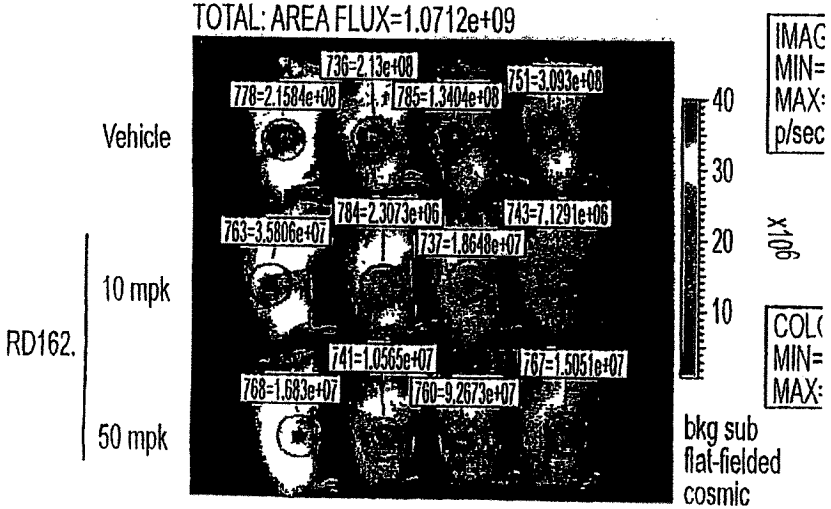


FIG. 12B

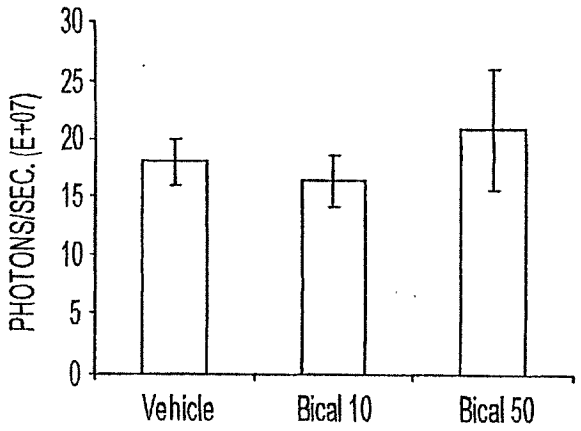


FIG. 12C

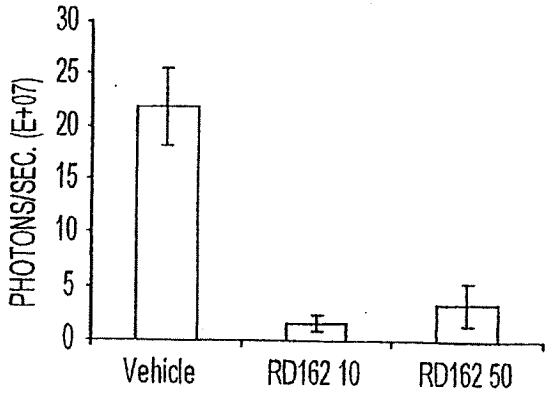


FIG. 12D

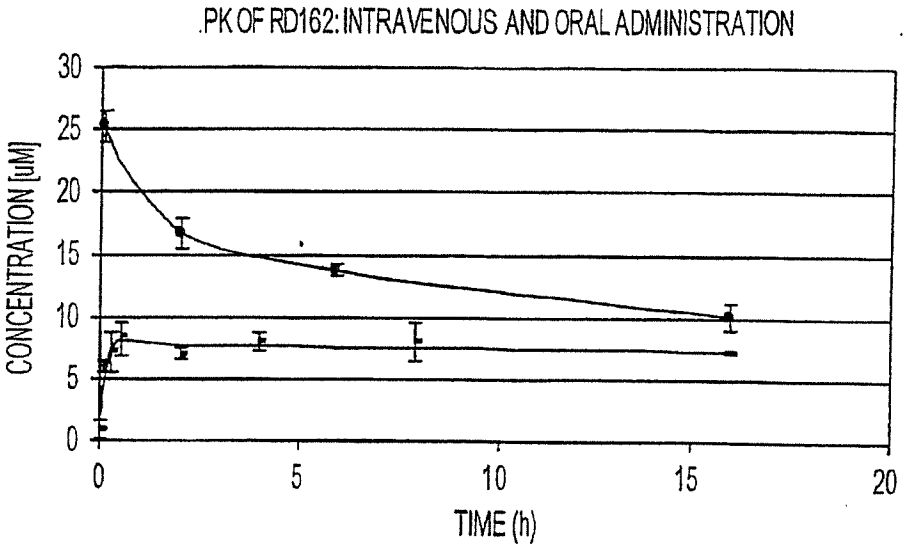

PK OF RD162: INTRAVENOUS AND ORAL ADMINISTRATION
CONCENTRATION [uM]
30
25
20
15
10
5
0
0
5
10
15
20
TIME (h)

FIG. 13

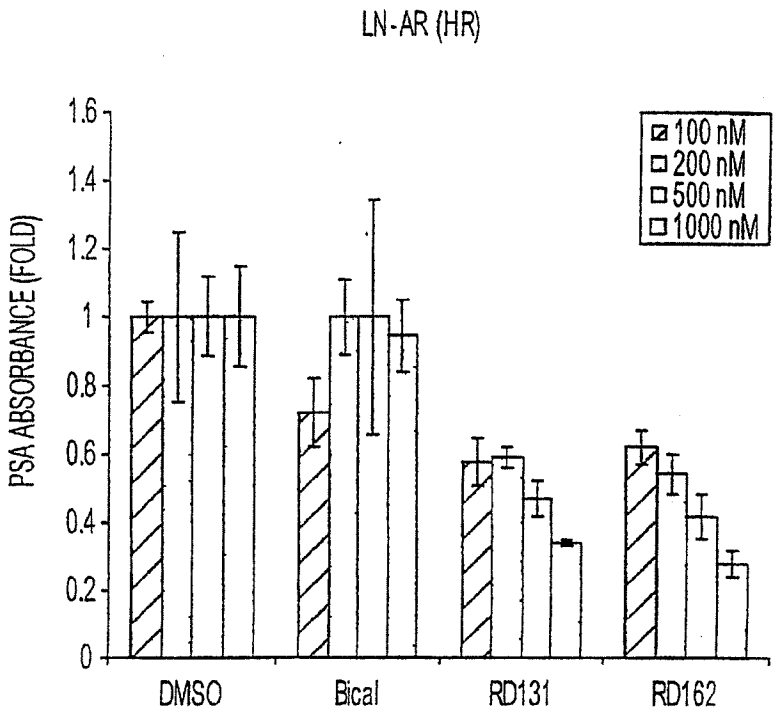

LN-AR (HR)
PSA ABSORBANCE (FOLD)
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
100 nM
200 nM
500 nM
1000 nM
DMSO
Bical
RD131
RD162

FIG. 14

CHARACTERISTICS OF Bicalutimide, RD37, RD131 AND RD162

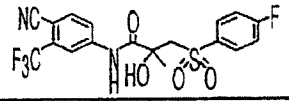
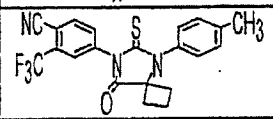
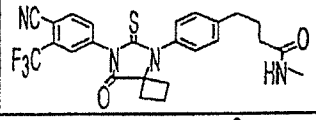
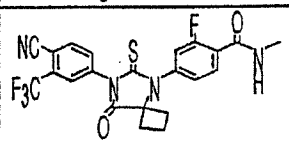
NAME	STRUCTURE	IC_{50} [nM]	LogP	C_{SS},10mpk [μM]	C_{SS},25mpk [μM]	C_{SS},50mpk [μM]
Bic.		1000	2.91	10.0	11.4	11.9
RD37		124	4.20	NA	NA	NA
RD131		92	3.44	0.39	0.43	0.40
RD162		122	3.20	9.9	10.7	10.2

FIG. 15A

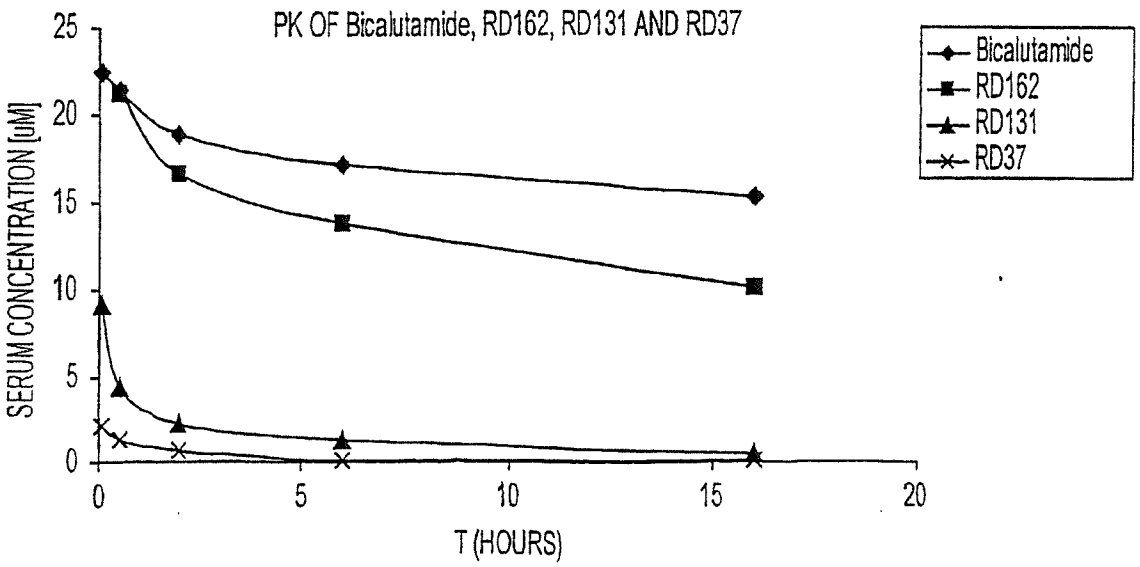


FIG. 15B

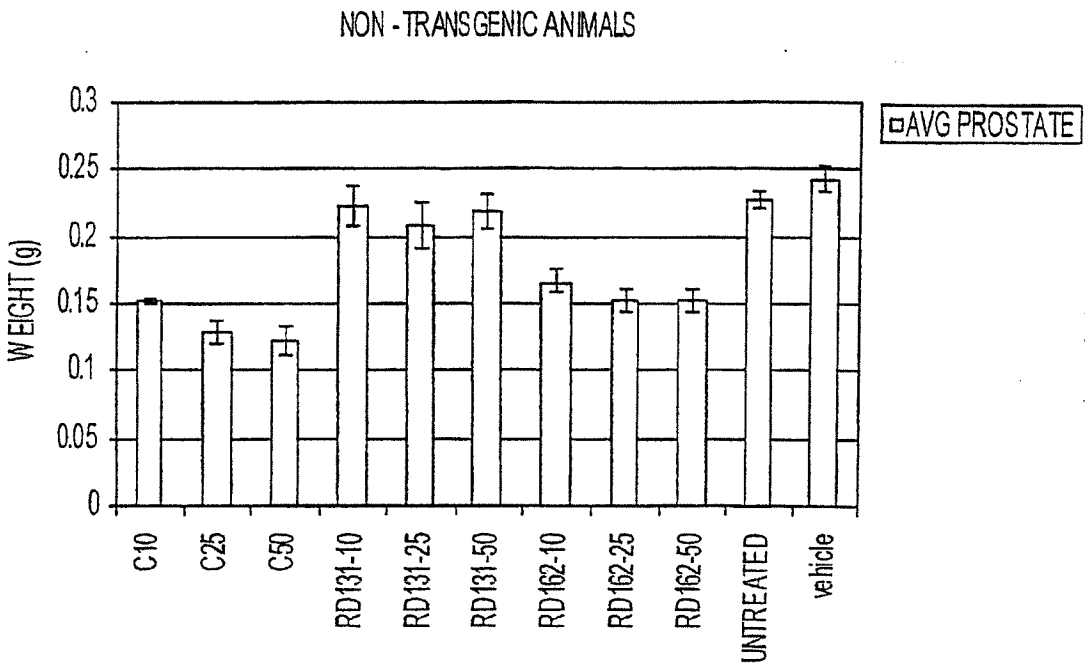

NON - TRANSGENIC ANIMALS
WEIGHT (g)
0.3
0.25
0.2
0.15
0.1
0.05
0
AVG PROSTATE
C10
C25
C50
RD131-10
RD131-25
RD131-50
RD162-10
RD162-25
RD162-50
UNTREATED
vehicle

FIG. 16

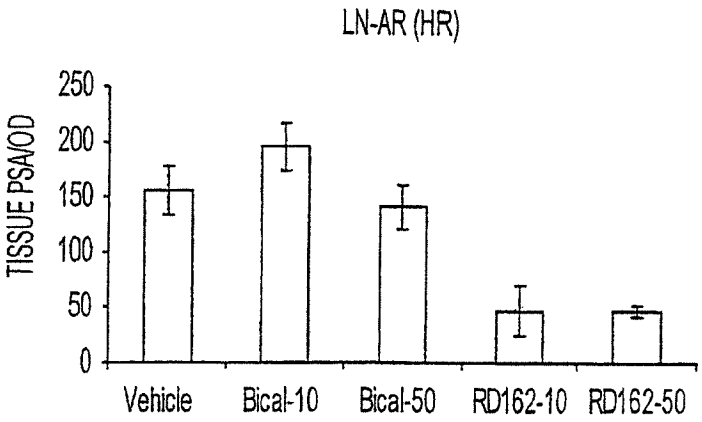

LN-AR (HR)
TISSUE PSA/OD
250
200
150
100
50
0
Vehicle
Bical-10
Bical-50
RD162-10
RD162-50

FIG. 17

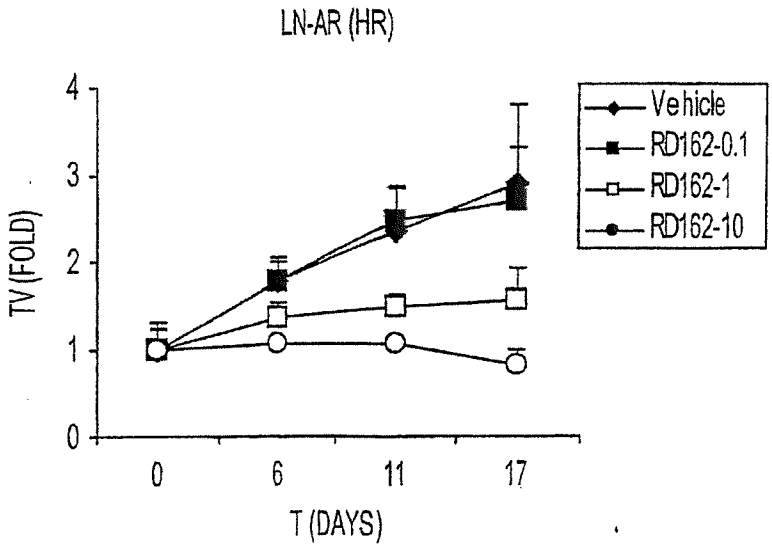

LN-AR (HR)
TV (FOLD)
4
3
2
1
0
0
6
11
17
T (DAYS)
Vehicle
RD162-0.1
RD162-1
RD162-10

FIG. 18

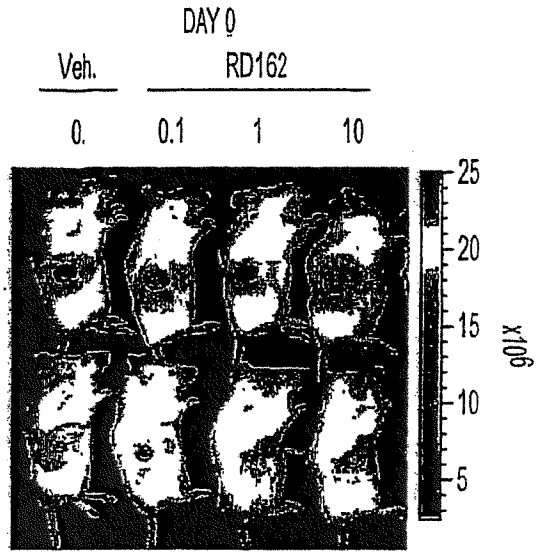


FIG. 19A

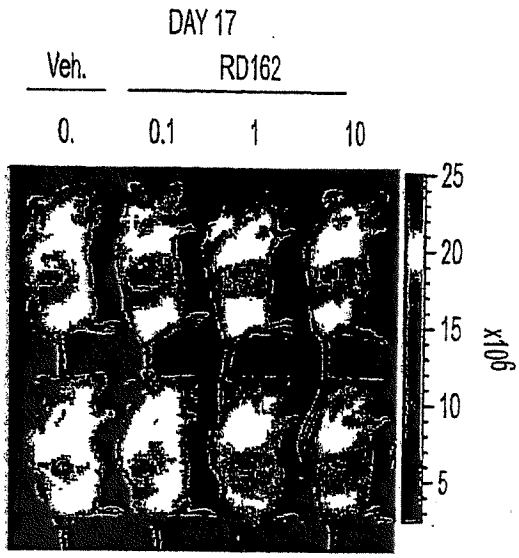


FIG. 19B

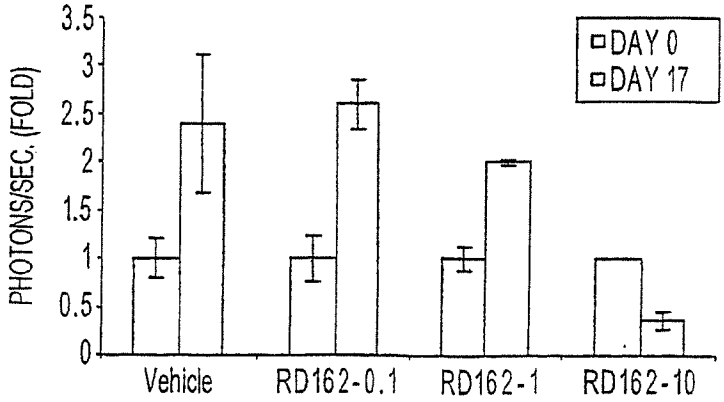


FIG. 19C

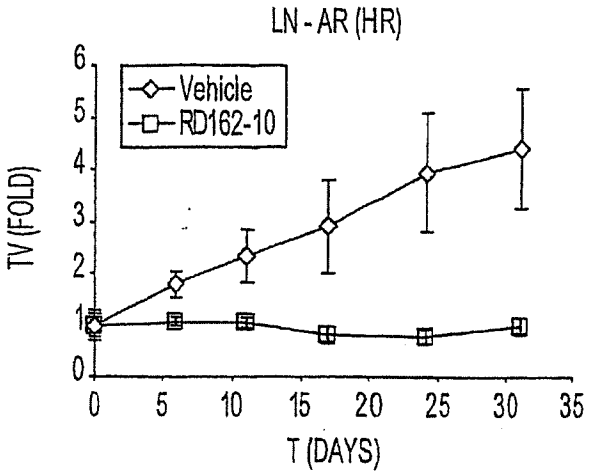


FIG. 20A

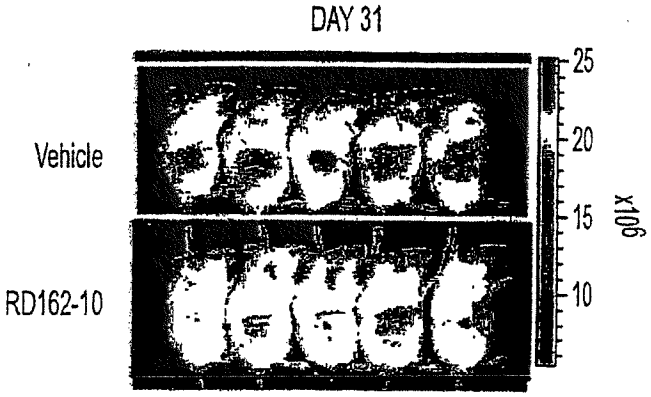


FIG. 20B

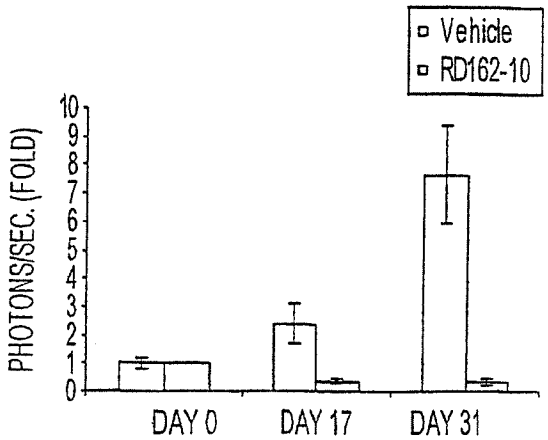


FIG. 20C

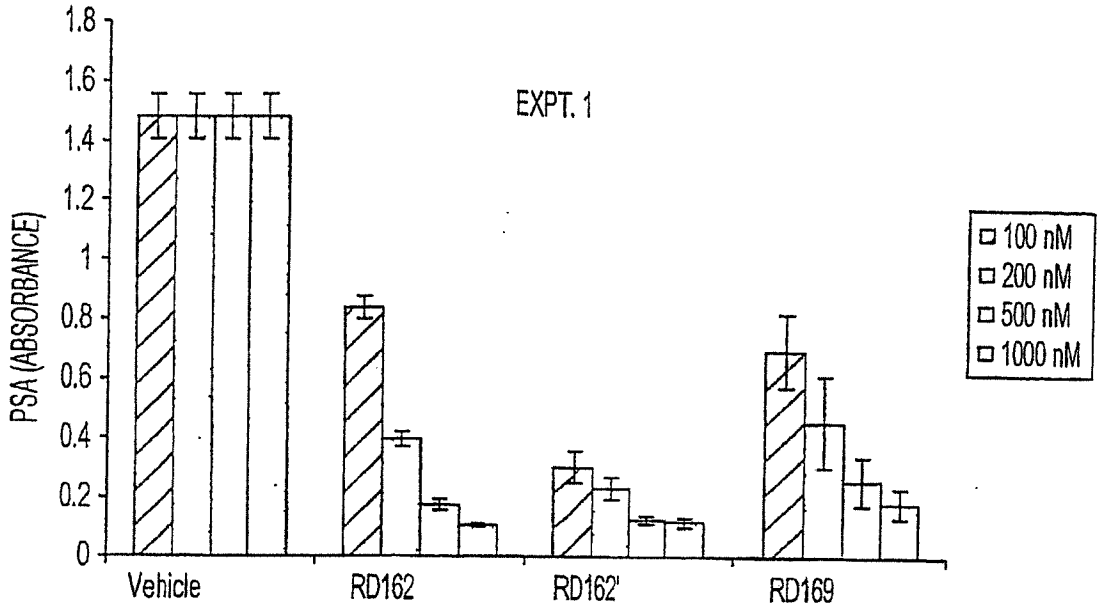


FIG. 21A

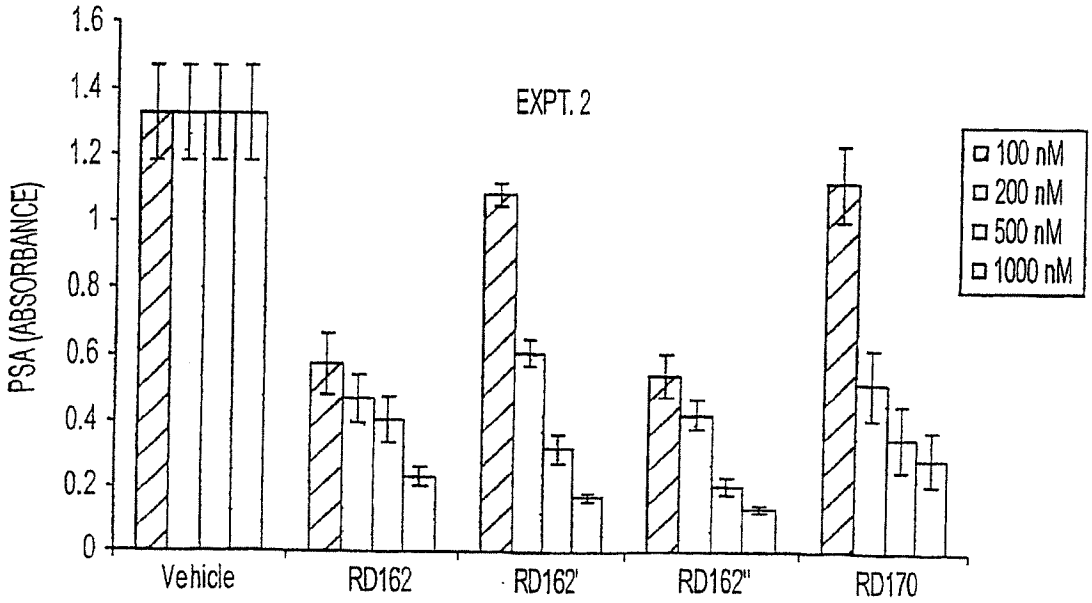


FIG. 21B

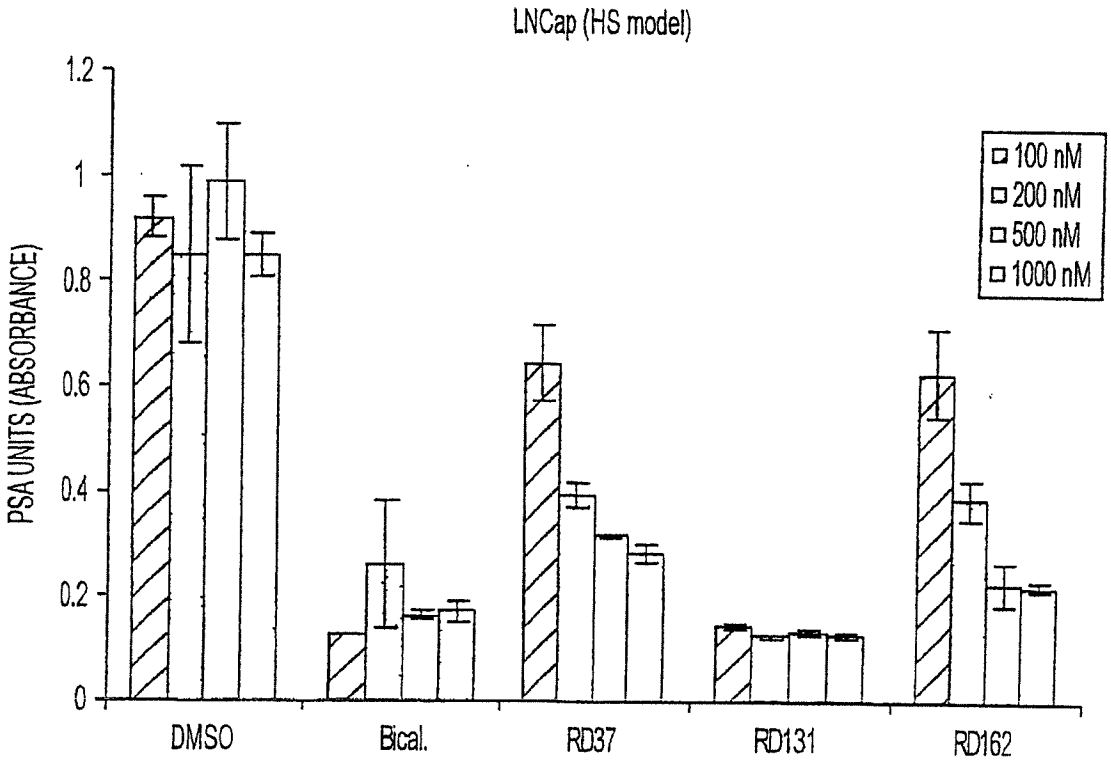

LNCap (HS model)
PSA UNITS (ABSORBANCE)
1.2
1
0.8
0.6
0.4
0.2
0
100 nM
200 nM
500 nM
1000 nM
DMSO
Bical.
RD37
RD131
RD162

FIG. 22

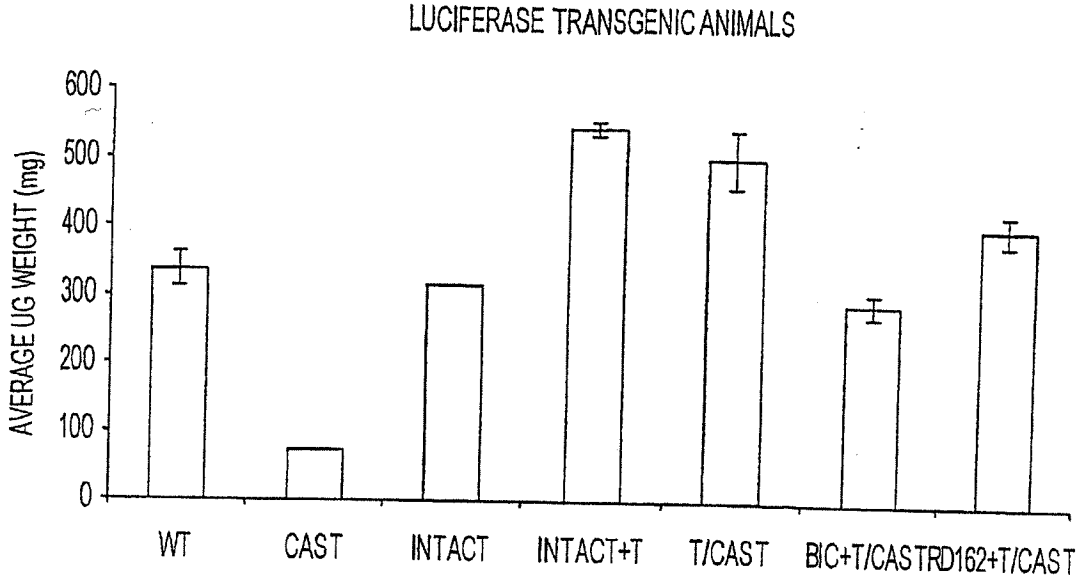


FIG. 23A

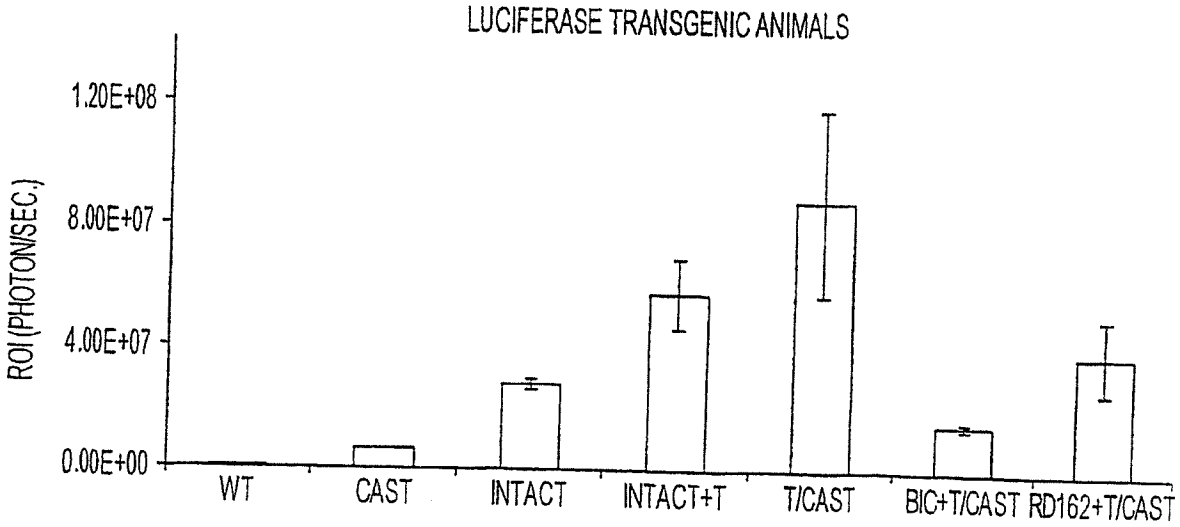


FIG. 23B

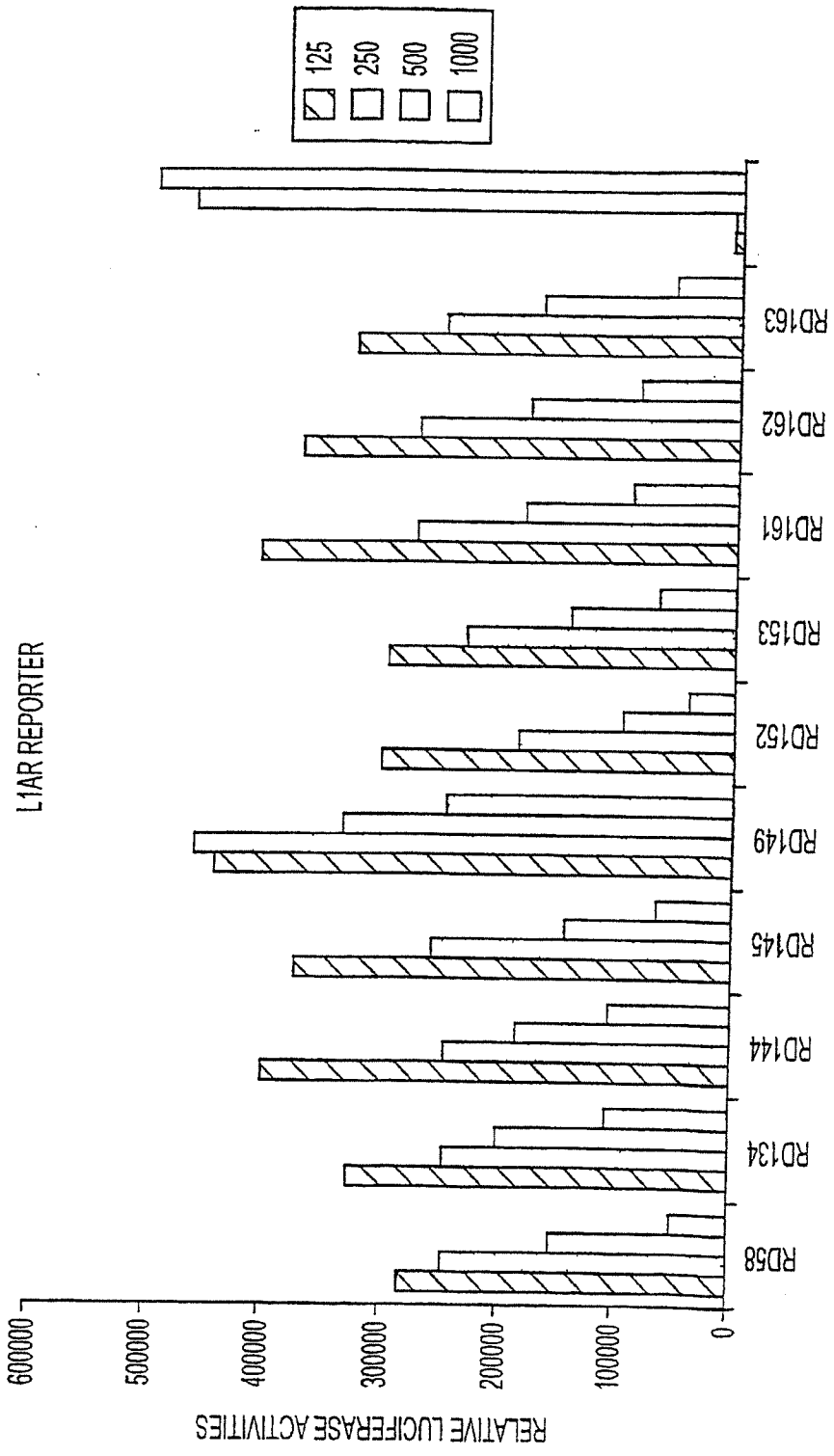

125
250
500
1000
RELATIVE LUCIFERASE ACTIVITIES
600000
500000
400000
300000
200000
100000
0
L1AR REPORTER
RD58
RD134
RD144
RD145
RD149
RD152
RD153
RD161
RD162
RD163

FIG. 24

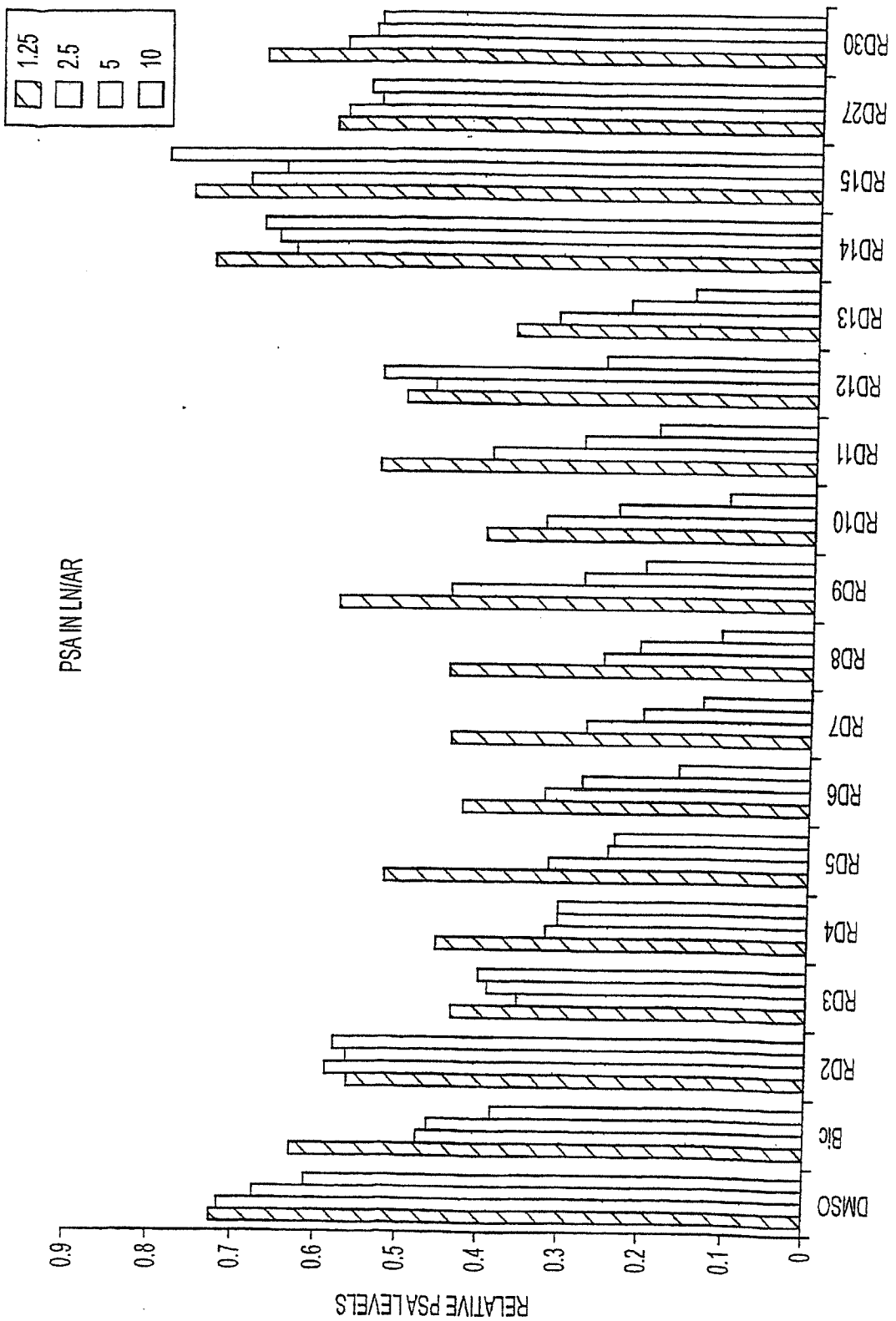

PSA IN LN/AR
1.25
2.5
5
10
RELATIVE PSA LEVELS
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
DMSO
Bic
RD2
RD3
RD4
RD5
RD6
RD7
RD8
RD9
RD10
RD11
RD12
RD13
RD14
RD15
RD27
RD30

FIG. 25

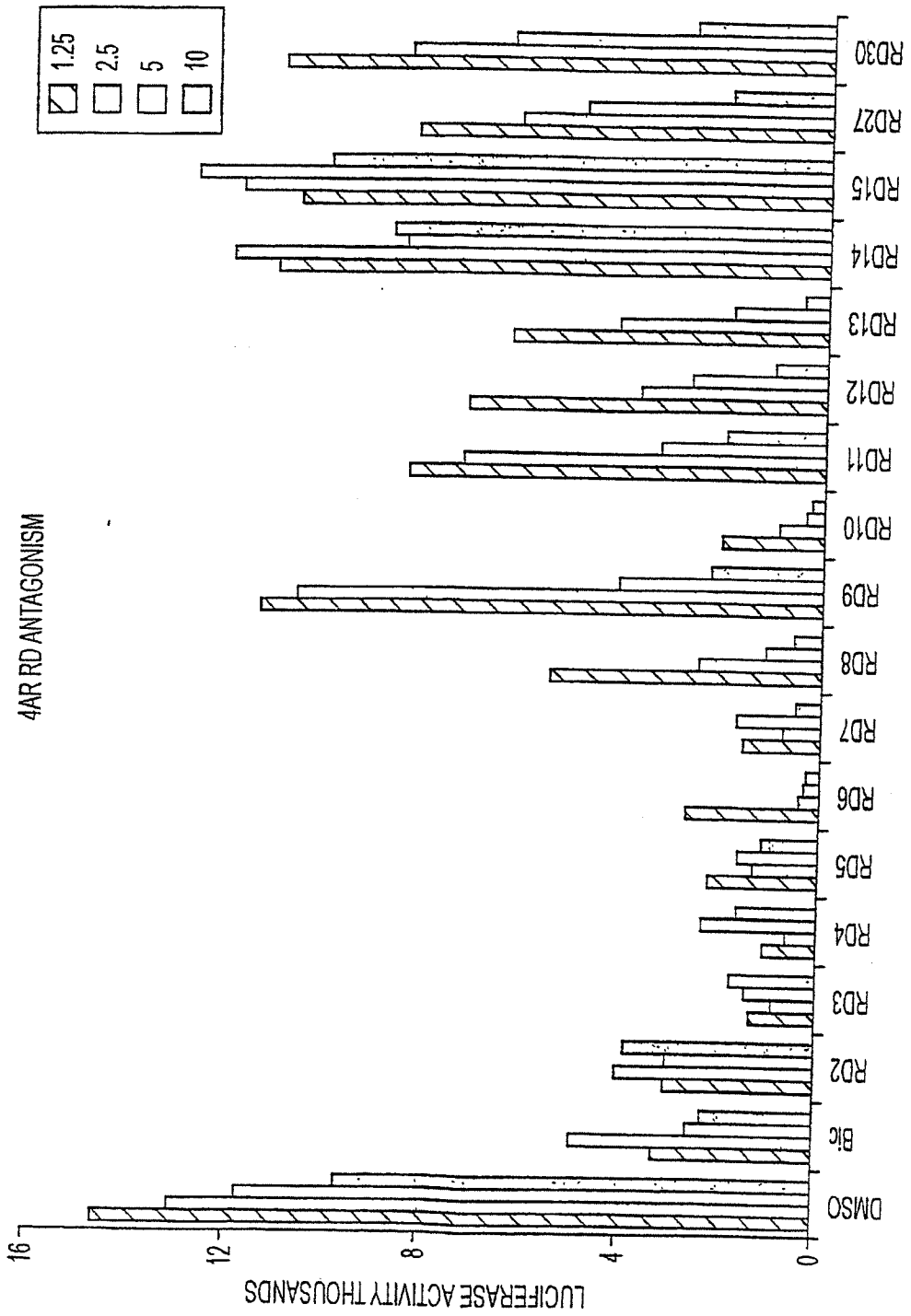

4AR RD ANTAGONISM
LUCIFERASE ACTIVITY THOUSANDS
16
12
8
4
0
1.25
2.5
5
10
DMSO
Bic
RD2
RD3
RD4
RD5
RD6
RD7
RD8
RD9
RD10
RD11
RD12
RD13
RD14
RD15
RD27
RD30

FIG. 26

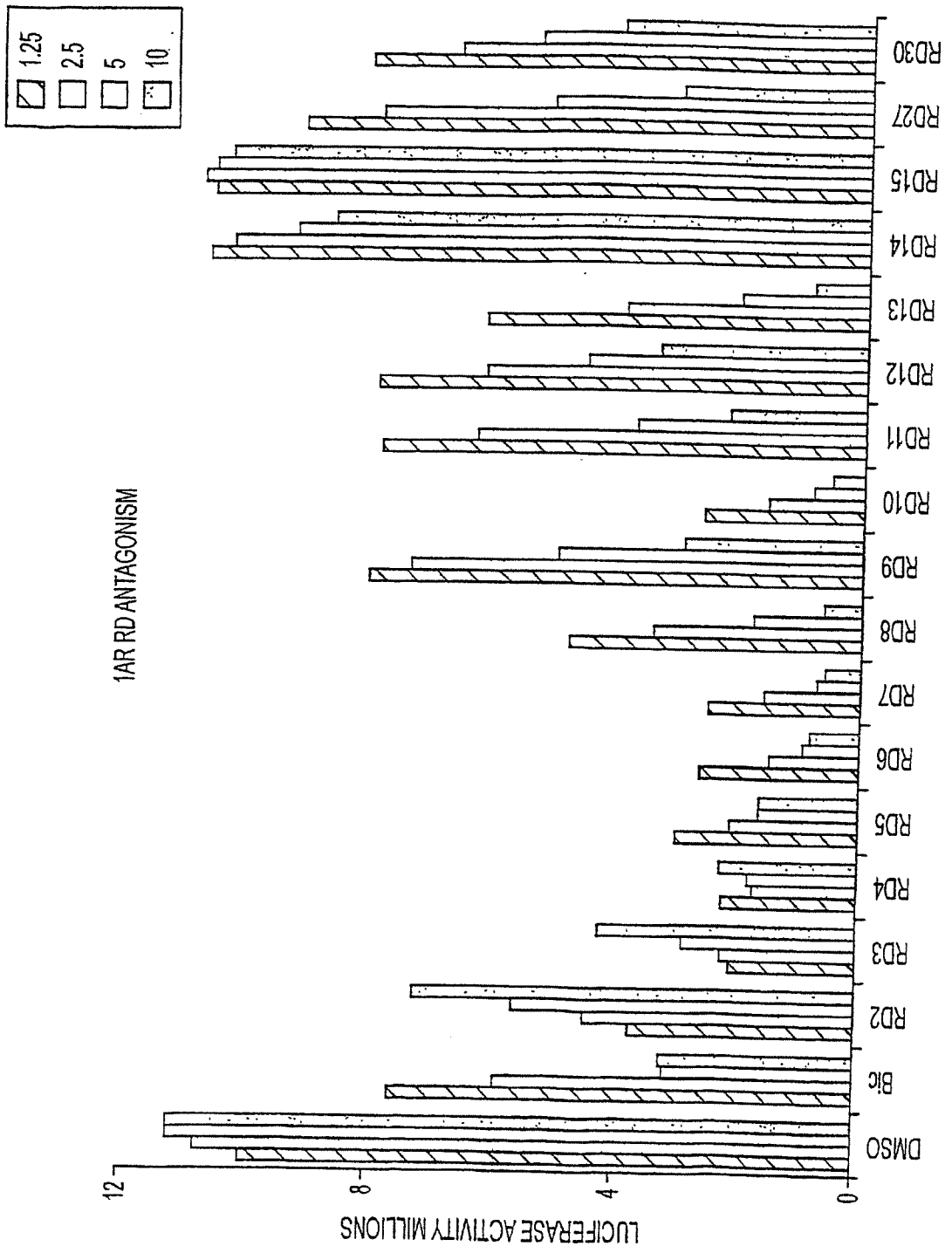

1AR RD ANTAGONISM
LUCIFERASE ACTIVITY MILLIONS
0
4
8
12
1.25
2.5
5
10
DMSO
Bic
RD2
RD3
RD4
RD5
RD6
RD7
RD8
RD9
RD10
RD11
RD12
RD13
RD14
RD15
RD27
RD30

FIG. 27

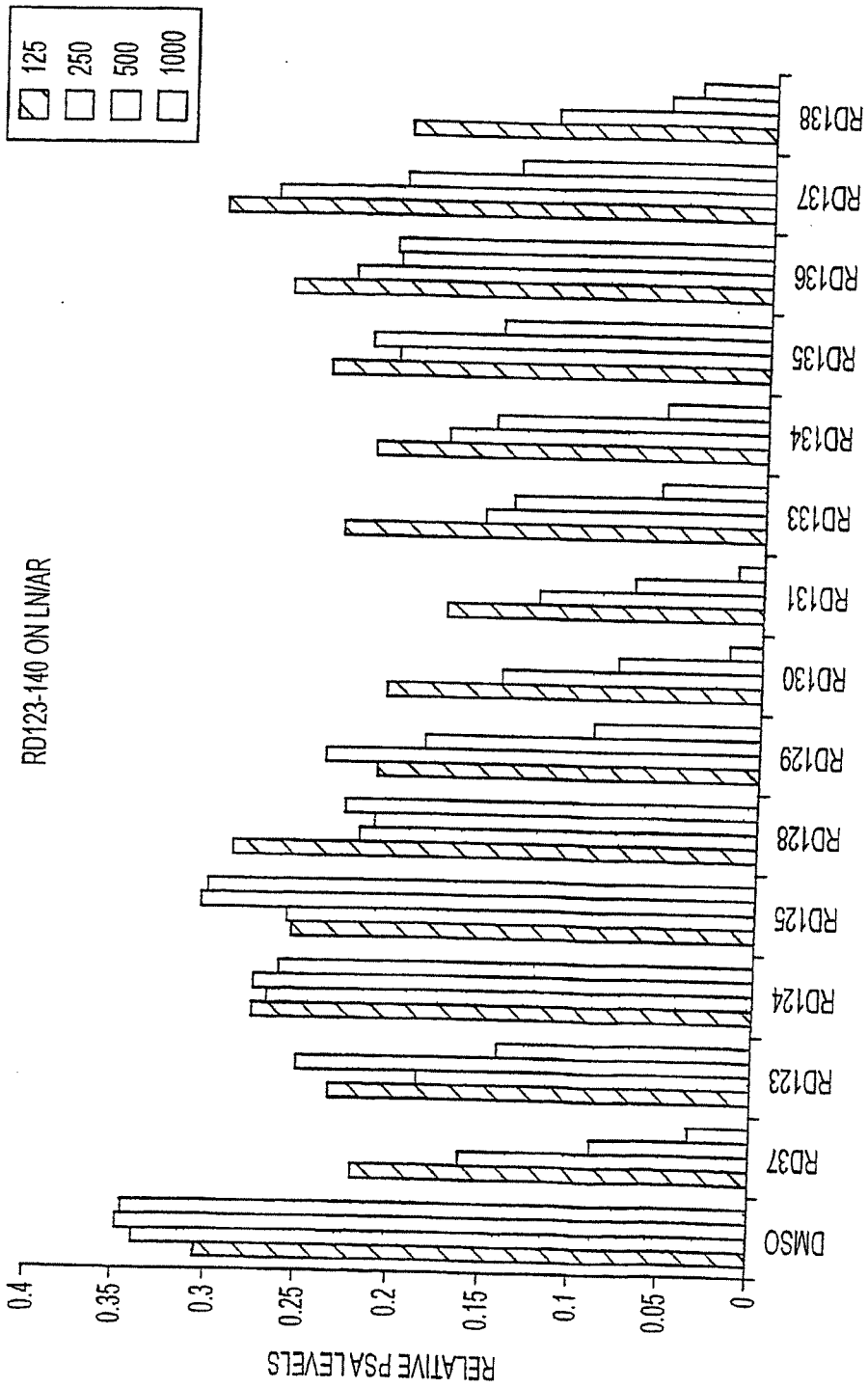

125
250
500
1000
RD123-140 ON LNAR
RELATIVE PSALEVELS
0.4
0.35
0.3
0.25
0.2
0.15
0.1
0.05
0
DMSO
RD37
RD123
RD124
RD125
RD128
RD129
RD130
RD131
RD133
RD134
RD135
RD136
RD137
RD138

FIG. 28

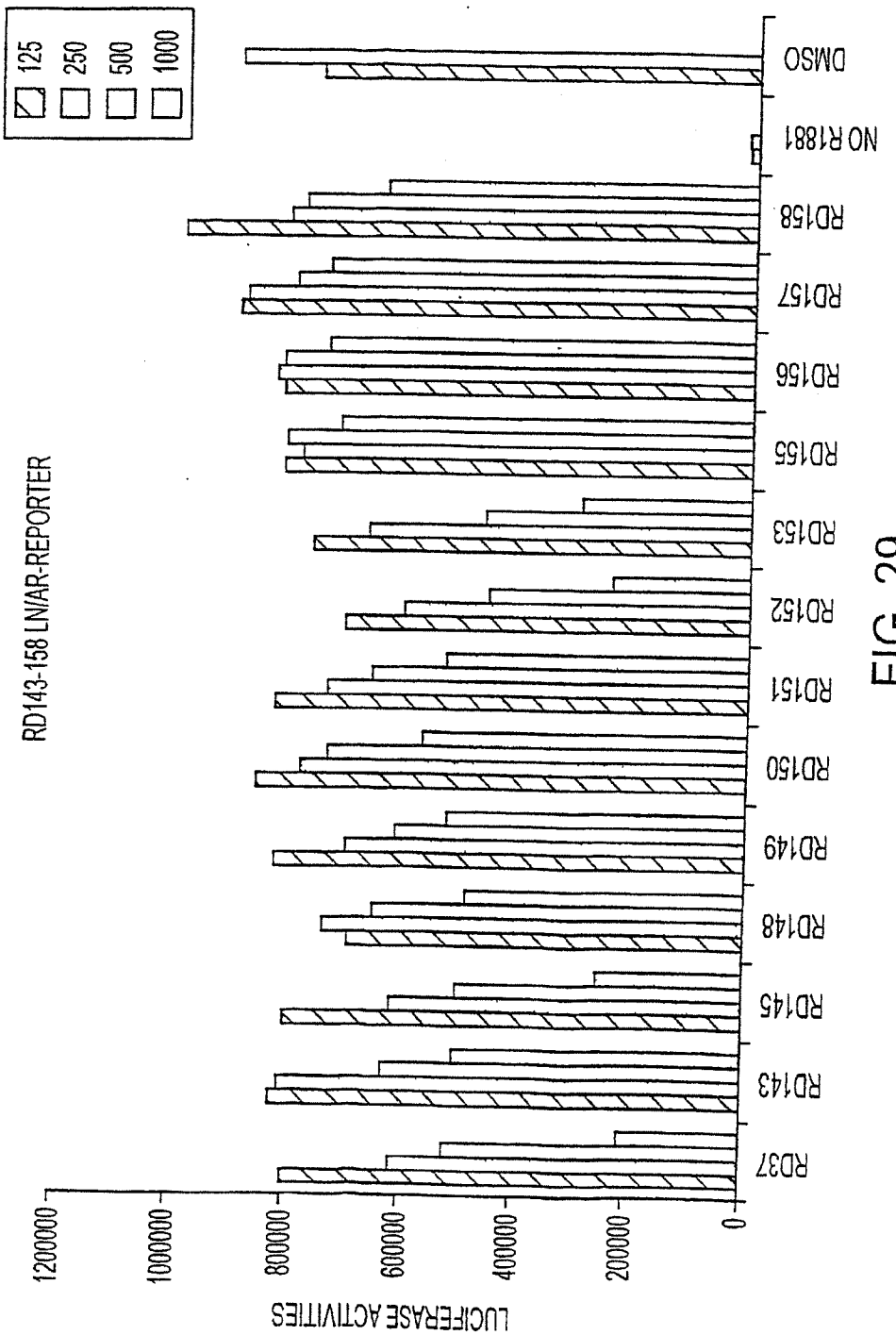

RD143-158 LNIAR-REPORTER
125
250
500
1000
LUCIFERASE ACTIVITIES
1200000
1000000
800000
600000
400000
200000
0
RD37
RD143
RD145
RD148
RD149
RD150
RD151
RD152
RD153
RD155
RD156
RD157
RD158
NO R1881
DMSO

FIG. 29