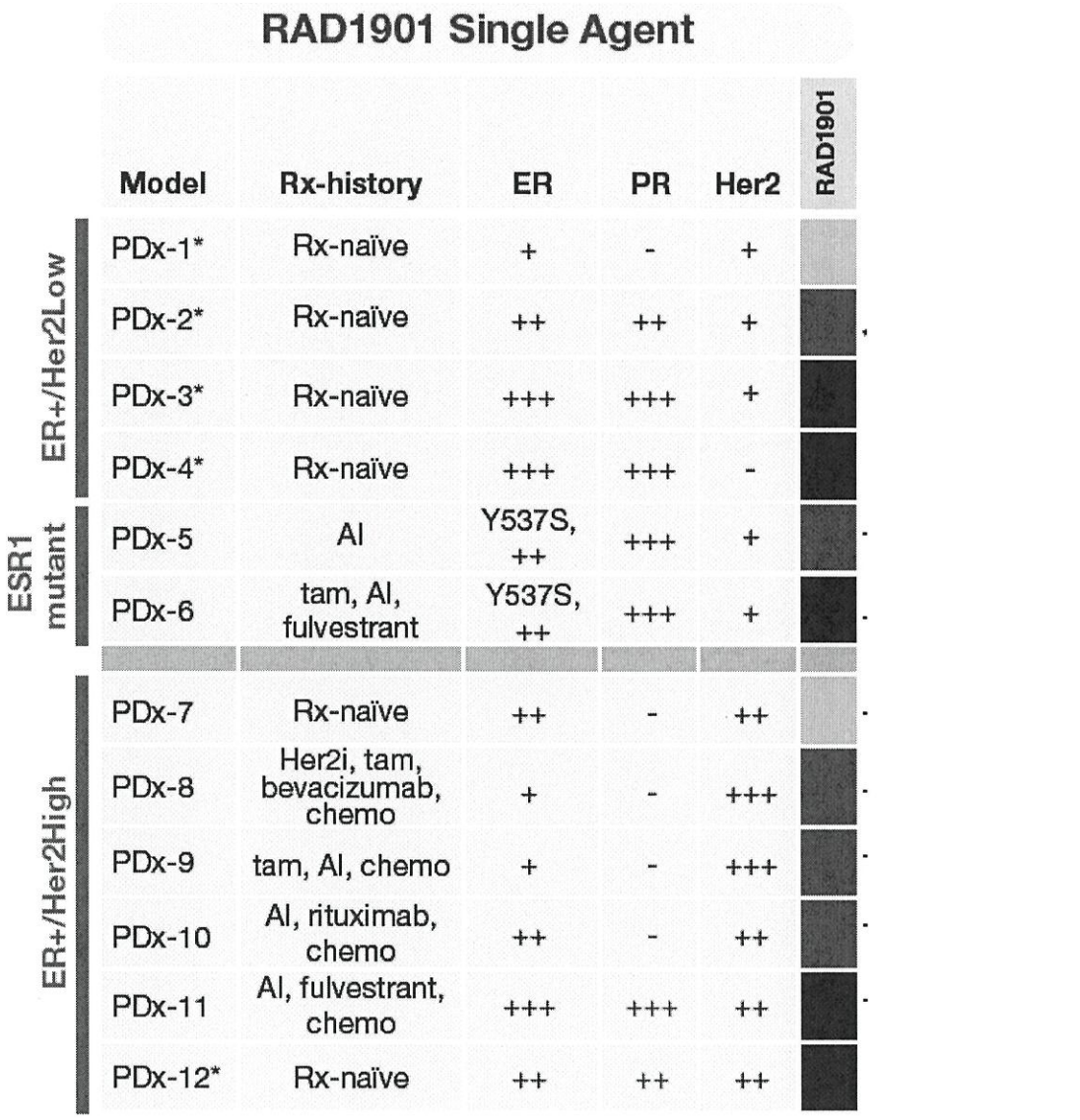
Fig. 1



AI: aromatase inhibitor;
tam: tamoxifen;
chemo: chemotherapy;
Her2i: trastuzumab, lapatinib;
Rx-naïve: Treatment naïve

RAD1901, po, qd
palbociclib, po, qd
Screen: n=3
*Full efficacy study n=8-10

Tumor growth inhibition (TGI) = (1-[Mean tumor volume of RAD1901 group/Mean tumor volume of control group])*100

Fig. 2A

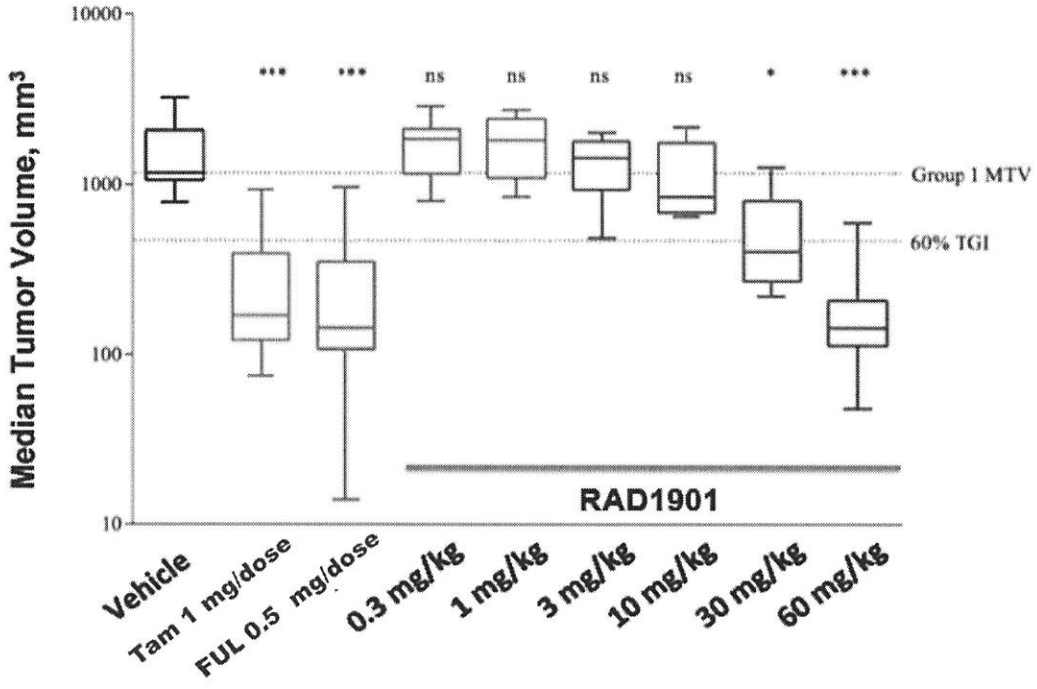

Median Tumor Volume, mm³
10000
1000
100
10
*** *** ns ns ns ns * ***
Group 1 MTV
60% TGI
RAD1901
Vehicle
Tam 1 mg/dose
FUL 0.5 mg/dose
0.3 mg/kg
1 mg/kg
3 mg/kg
10 mg/kg
30 mg/kg
60 mg/kg

Fig. 2B

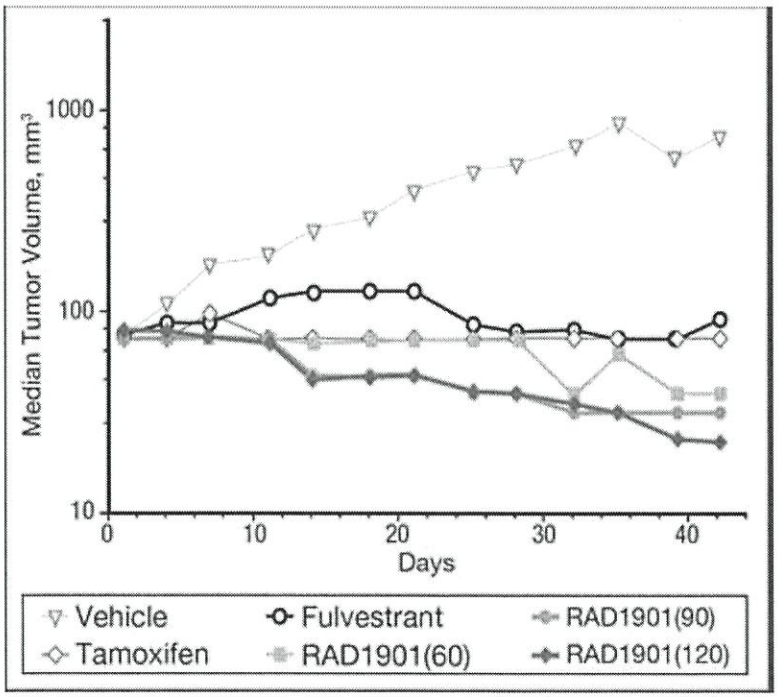

Median Tumor Volume, mm³
1000
100
10
0
10
20
30
40
Days
Vehicle
Fulvestrant
RAD1901(90)
Tamoxifen
RAD1901(60)
RAD1901(120)

Fig. 2C

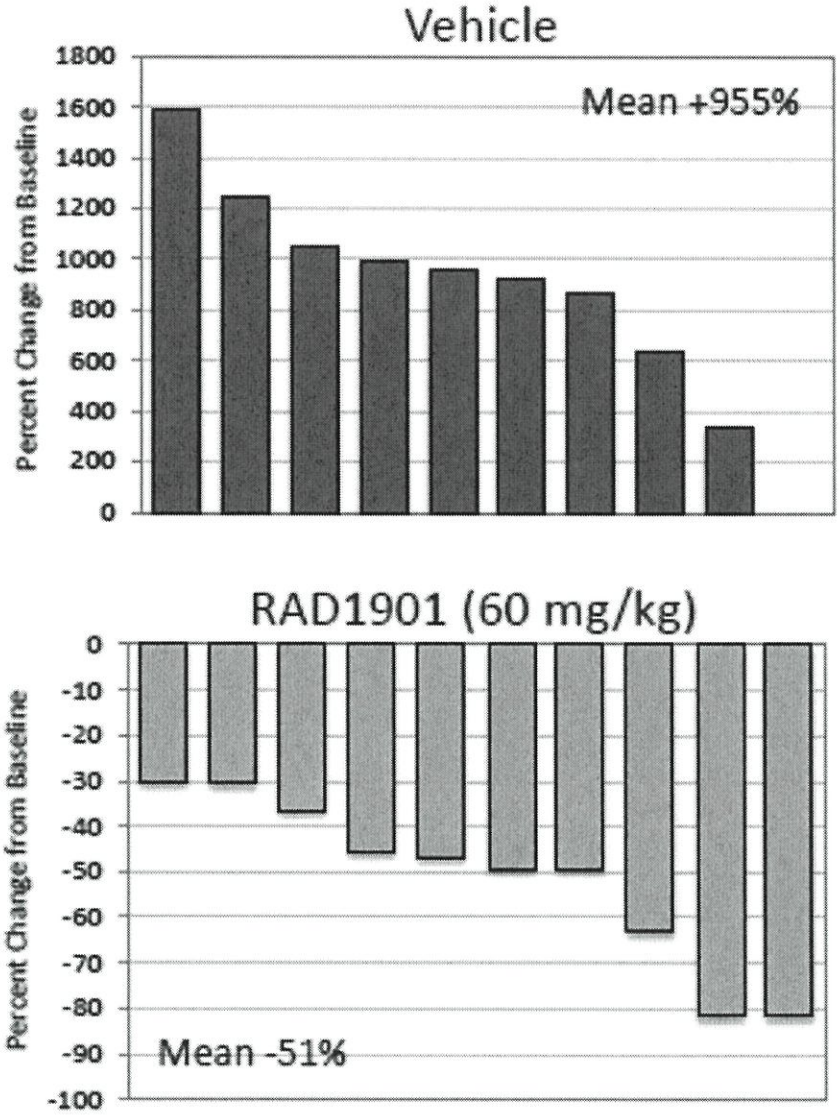

Vehicle
Mean +955%
Percent Change from Baseline
1800
1600
1400
1200
1000
800
600
400
200
0
RAD1901 (60 mg/kg)
Mean -51%
Percent Change from Baseline
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100

Fig. 2C (continued)

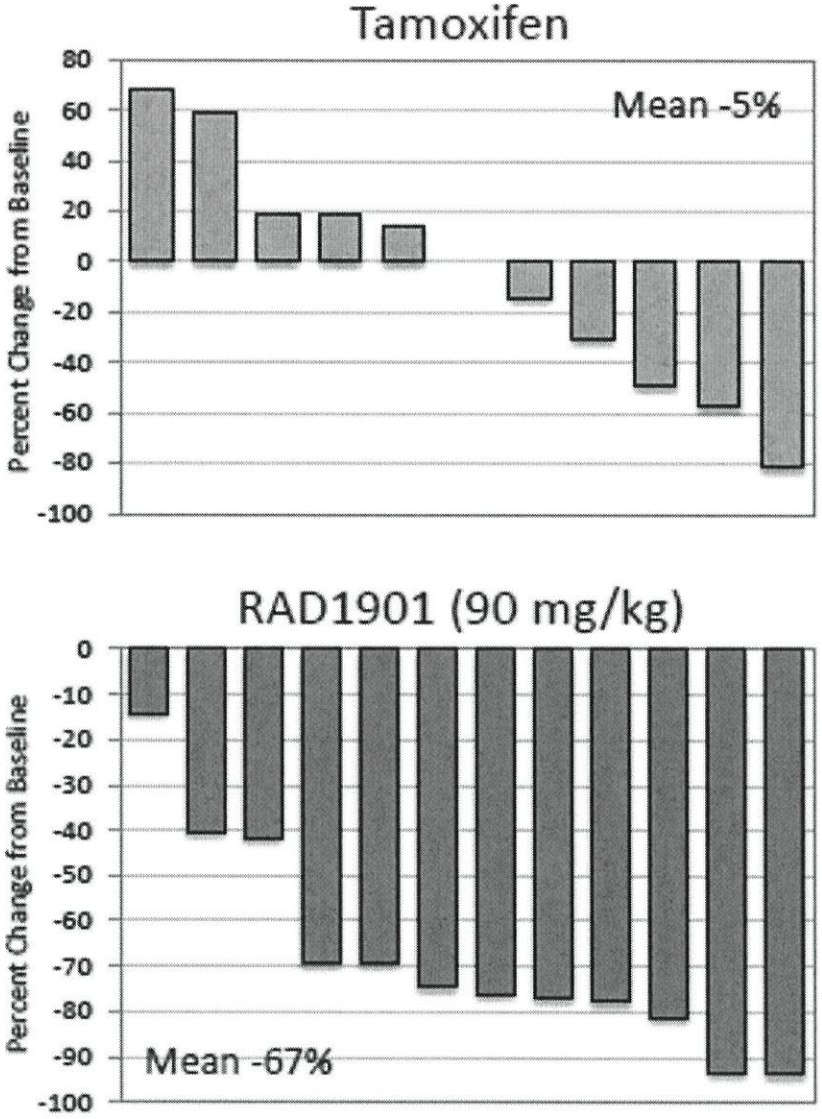


Fig. 2C (continued)

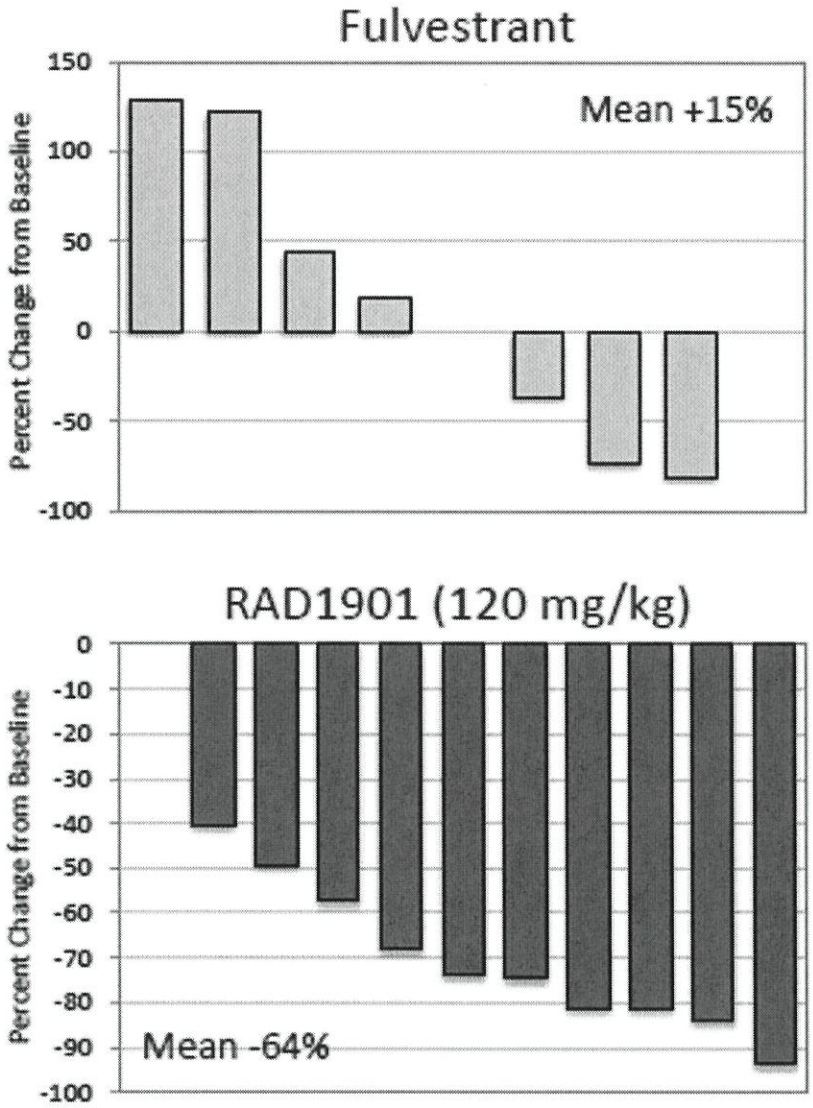


Fig. 2D

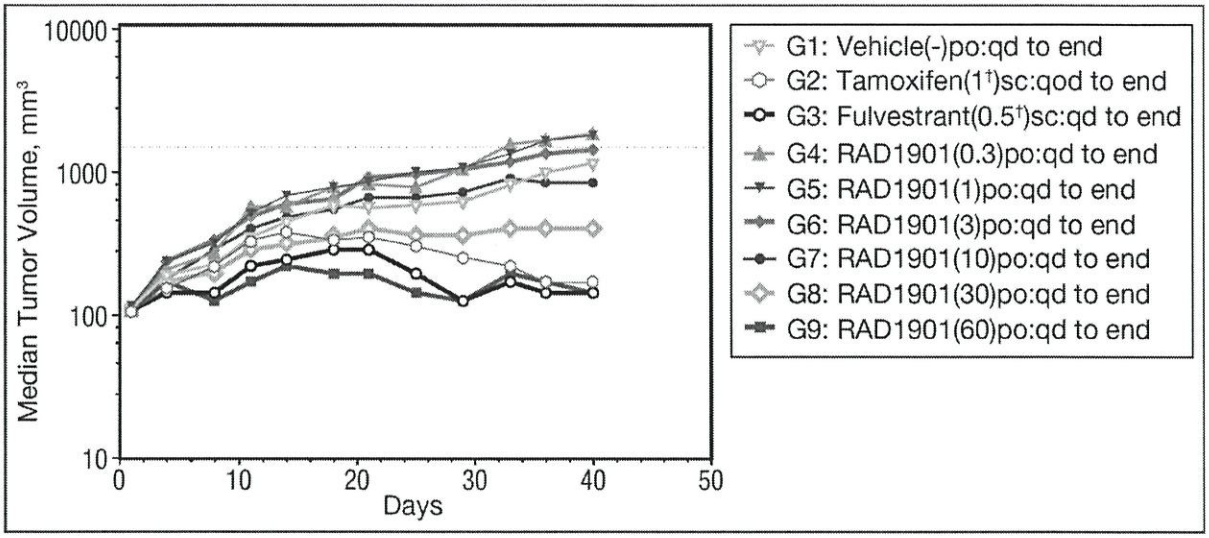

Median Tumor Volume, mm3
10000
1000
100
10
0
10
20
30
40
50
Days
G1: Vehicle(-)po:qd to end
G2: Tamoxifen(1†)sc:qod to end
G3: Fulvestrant(0.5†)sc:qd to end
G4: RAD1901(0.3)po:qd to end
G5: RAD1901(1)po:qd to end
G6: RAD1901(3)po:qd to end
G7: RAD1901(10)po:qd to end
G8: RAD1901(30)po:qd to end
G9: RAD1901(60)po:qd to end

Fig. 2E

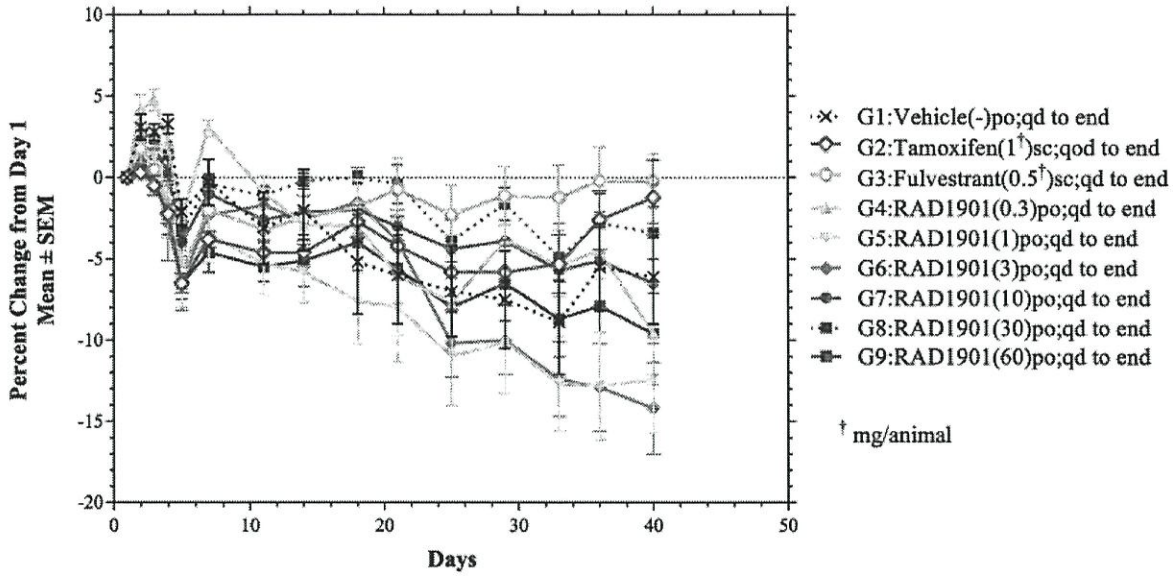

Percent Change from Day 1
Mean ± SEM
Days
10
5
0
-5
-10
-15
-20
0
10
20
30
40
50
G1:Vehicle(-)po;qd to end
G2:Tamoxifen(1†)sc;qod to end
G3:Fulvestrant(0.5†)sc;qd to end
G4:RAD1901(0.3)po;qd to end
G5:RAD1901(1)po;qd to end
G6:RAD1901(3)po;qd to end
G7:RAD1901(10)po;qd to end
G8:RAD1901(30)po;qd to end
G9:RAD1901(60)po;qd to end
† mg/animal

Fig. 4A

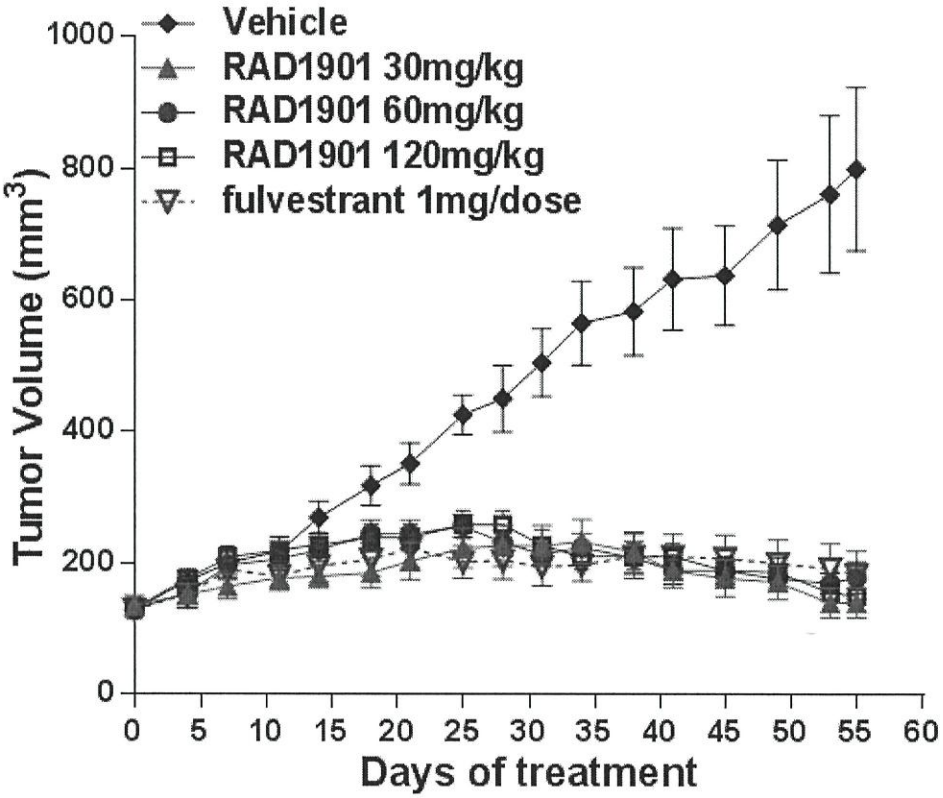

Vehicle
RAD1901 30mg/kg
RAD1901 60mg/kg
RAD1901 120mg/kg
fulvestrant 1mg/dose
Tumor Volume (mm3)
1000
800
600
400
200
0
0 5 10 15 20 25 30 35 40 45 50 55 60
Days of treatment

Fig. 4B

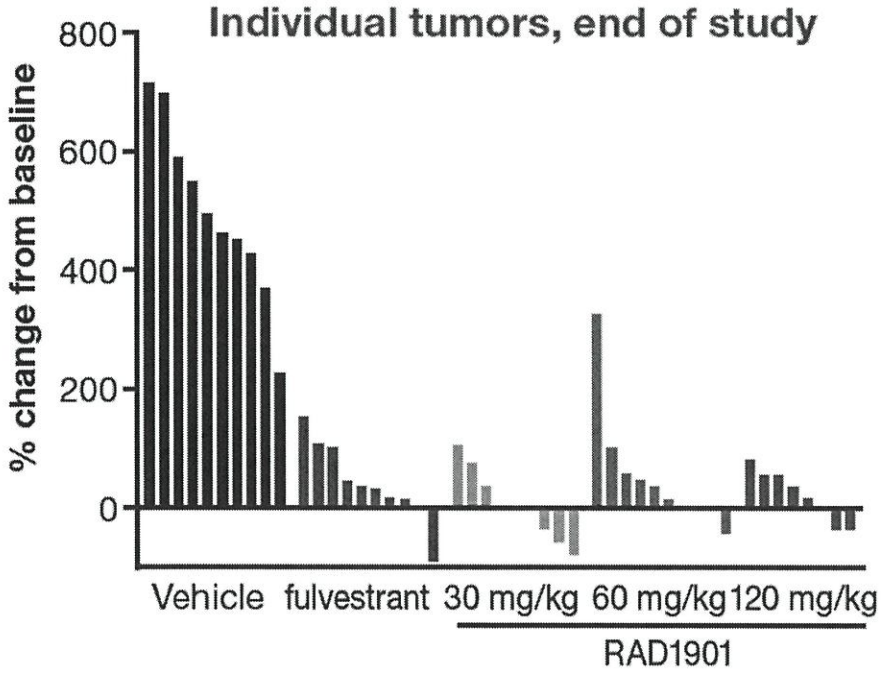

Individual tumors, end of study
% change from baseline
800
600
400
200
0
Vehicle
fulvestrant
30 mg/kg
60 mg/kg
120 mg/kg
RAD1901

Fig. 5

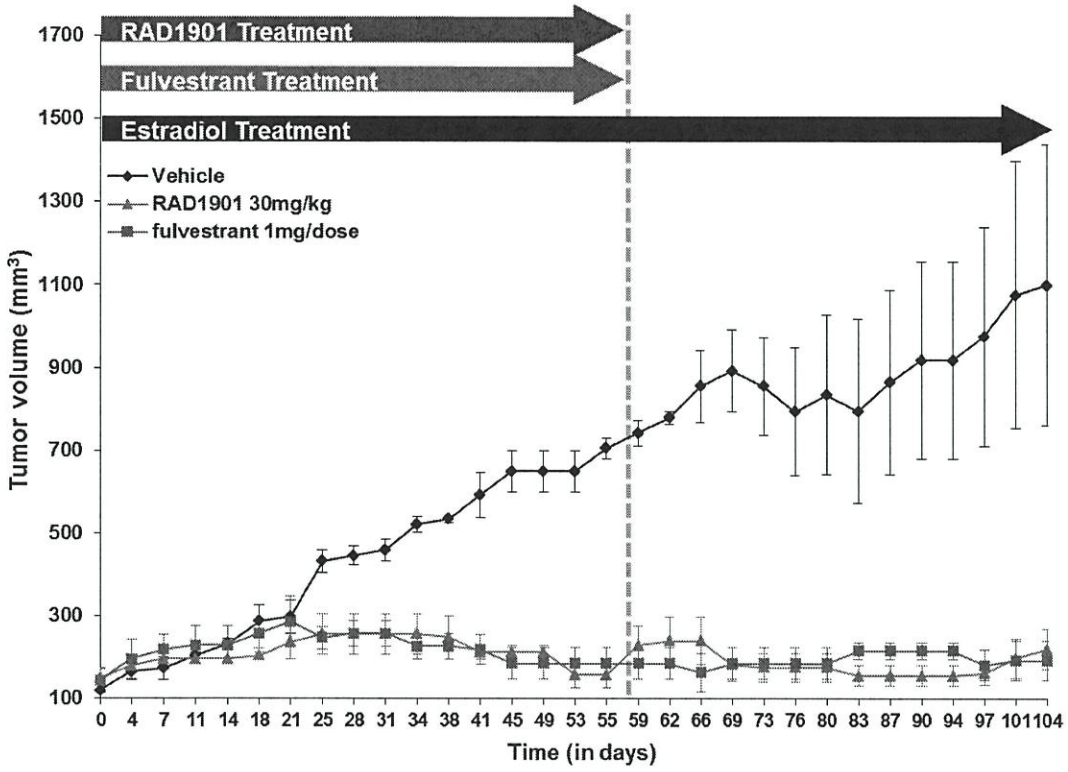

RAD1901 Treatment
Fulvestrant Treatment
Estradiol Treatment
Vehicle
RAD1901 30mg/kg
fulvestrant 1mg/dose
Tumor volume (mm3)
1700
1500
1300
1100
900
700
500
300
100
0 4 7 11 14 18 21 25 28 31 34 38 41 45 49 53 55 59 62 66 69 73 76 80 83 87 90 94 97 101104
Time (in days)

Fig. 7A

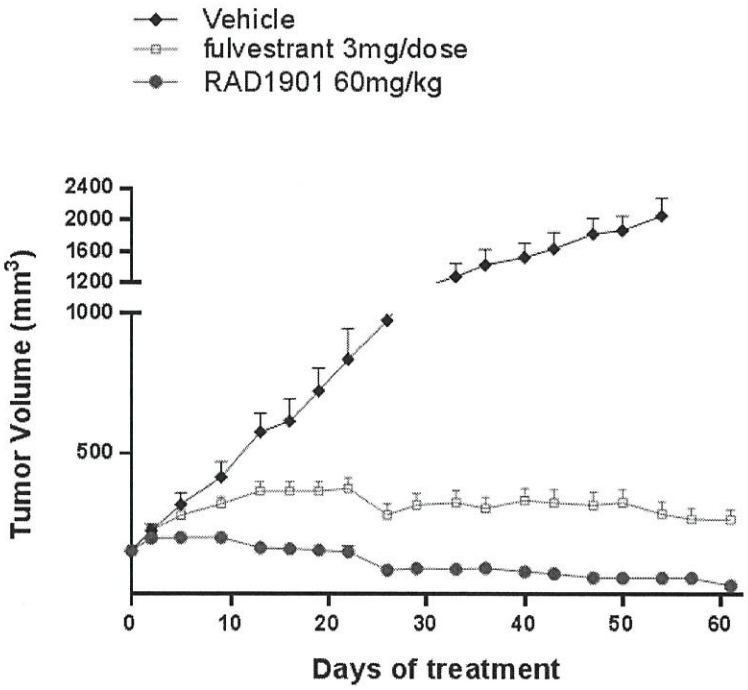

Vehicle
fulvestrant 3mg/dose
RAD1901 60mg/kg
Tumor Volume (mm3)
2400
2000
1600
1200
1000
500
0
10
20
30
40
50
60
Days of treatment

Fig. 7B

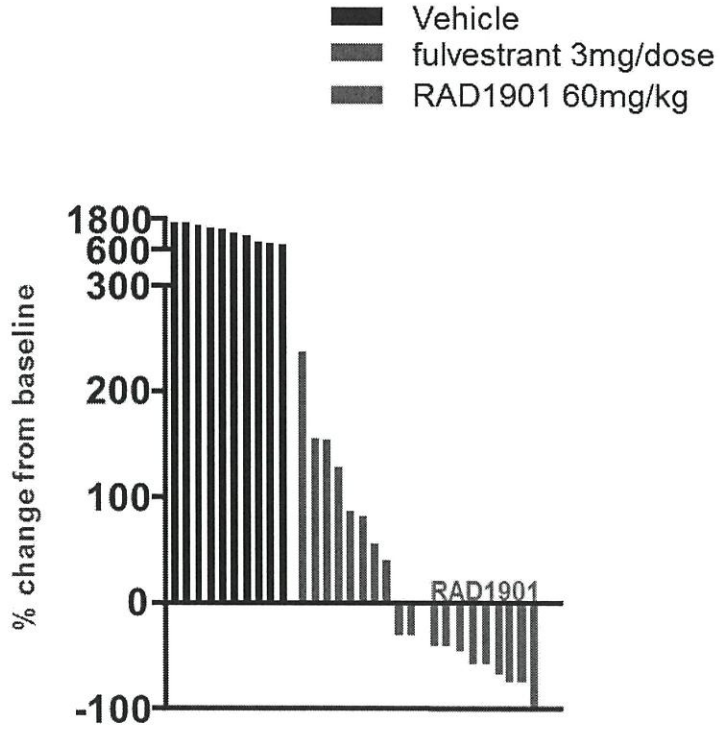

Vehicle
fulvestrant 3mg/dose
RAD1901 60mg/kg
% change from baseline
1800
600
300
200
100
0
-100
RAD1901

Fig. 8

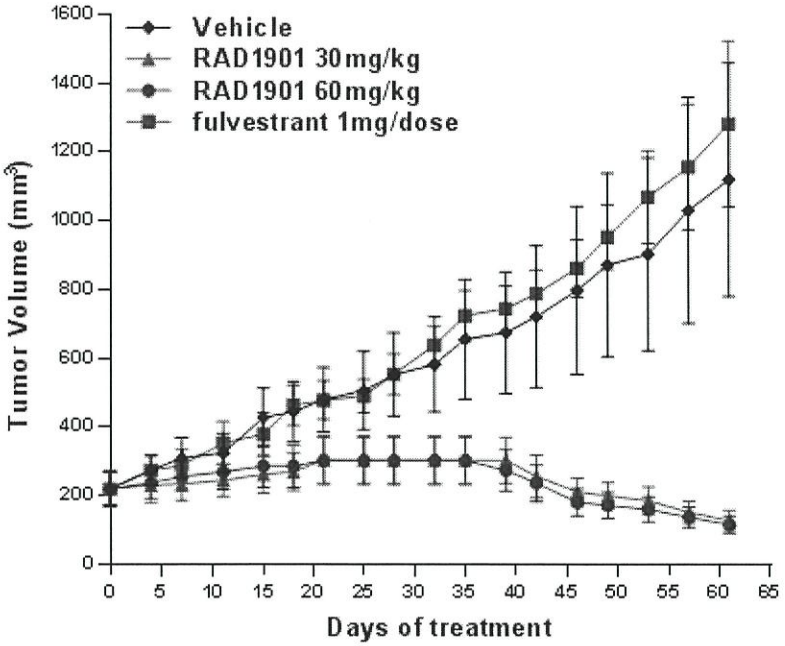

Vehicle
RAD1901 30mg/kg
RAD1901 60mg/kg
fulvestrant 1mg/dose
Tumor Volume (mm3)
Days of treatment
0
200
400
600
800
1000
1200
1400
1600
0
5
10
15
20
25
30
35
40
45
50
55
60
65

Fig. 13

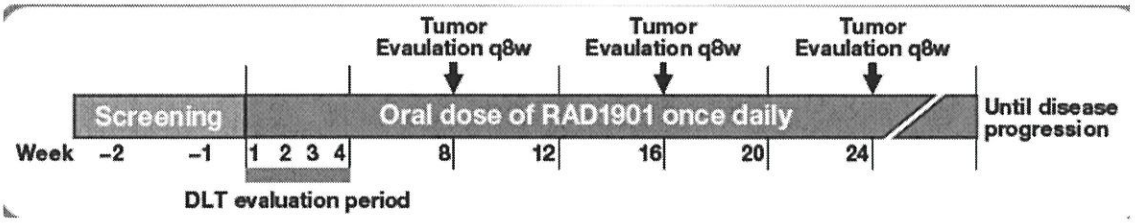
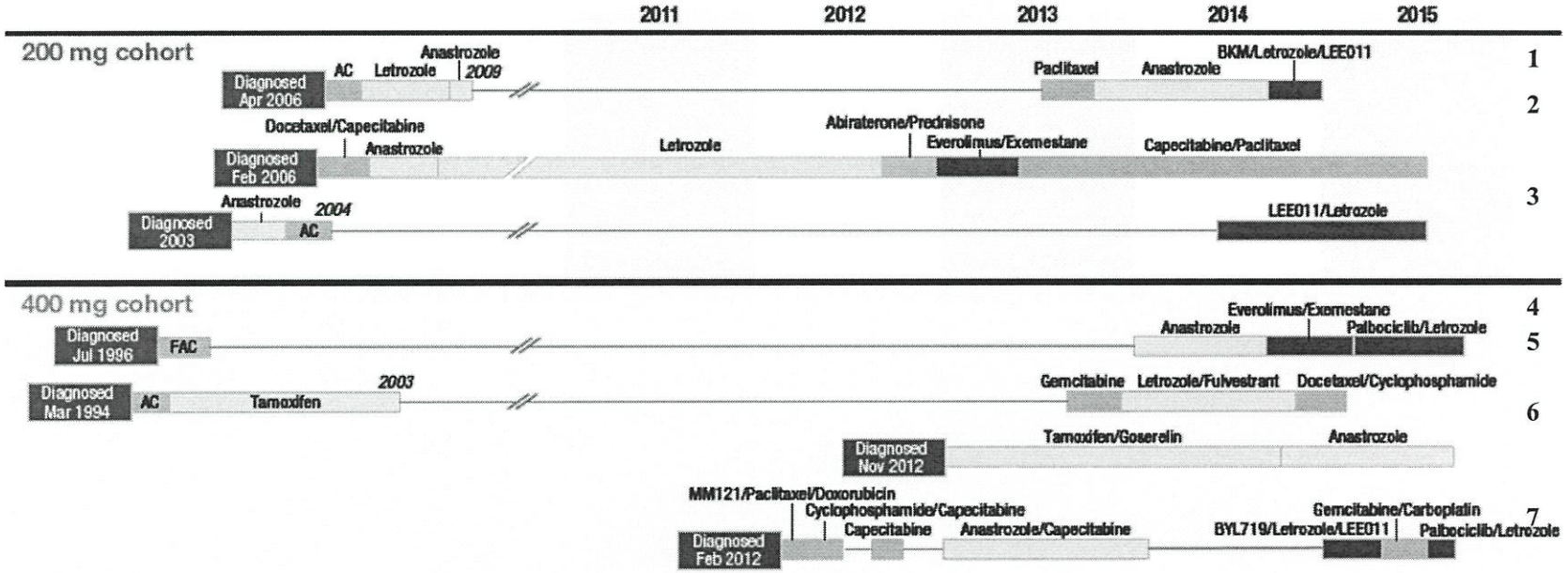

Tumor Evaulation q8w
Tumor Evaulation q8w
Tumor Evaulation q8w
Screening
Oral dose of RAD1901 once daily
Until disease progression
Week
-2
-1
1 2 3 4
8
12
16
20
24
DLT evaluation period

Fig. 14A

Subject No:



Abbreviations: AC, doxorubicin/cyclophosphomide; FAC, 5-fluorouracil/doxorubicin /cyclophosphamide

Fig. 14B

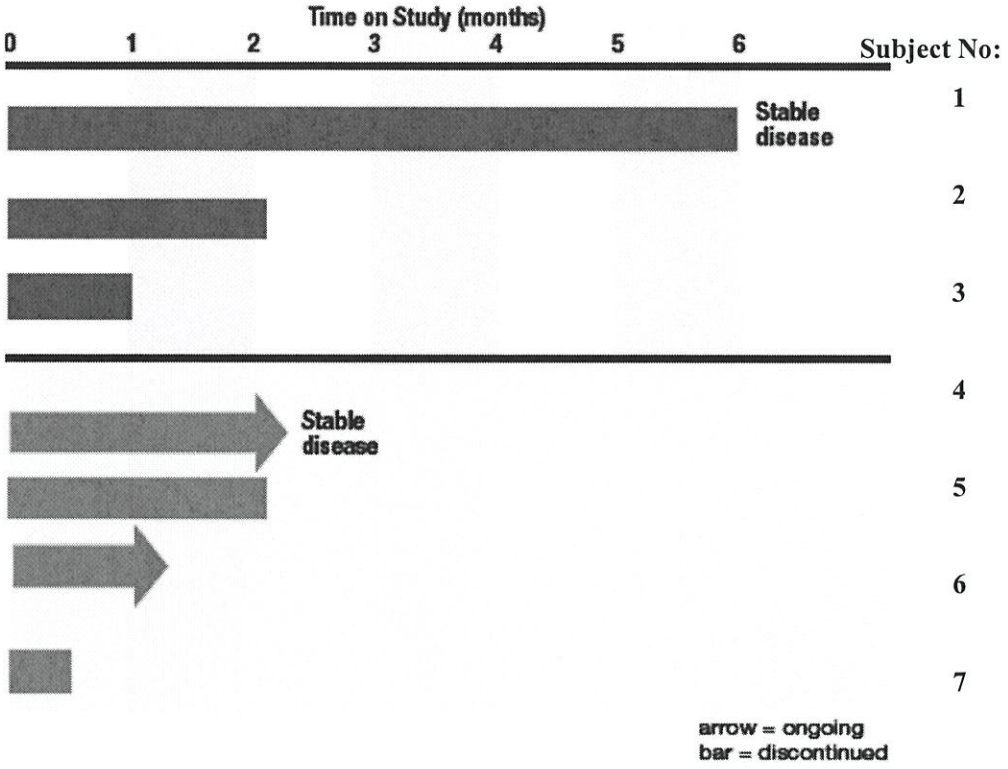

Time on Study (months)
0
1
2
3
4
5
6
Subject No:
1
Stable disease
2
3
4
Stable disease
5
6
7
arrow = ongoing
bar = discontinued

Fig. 17A

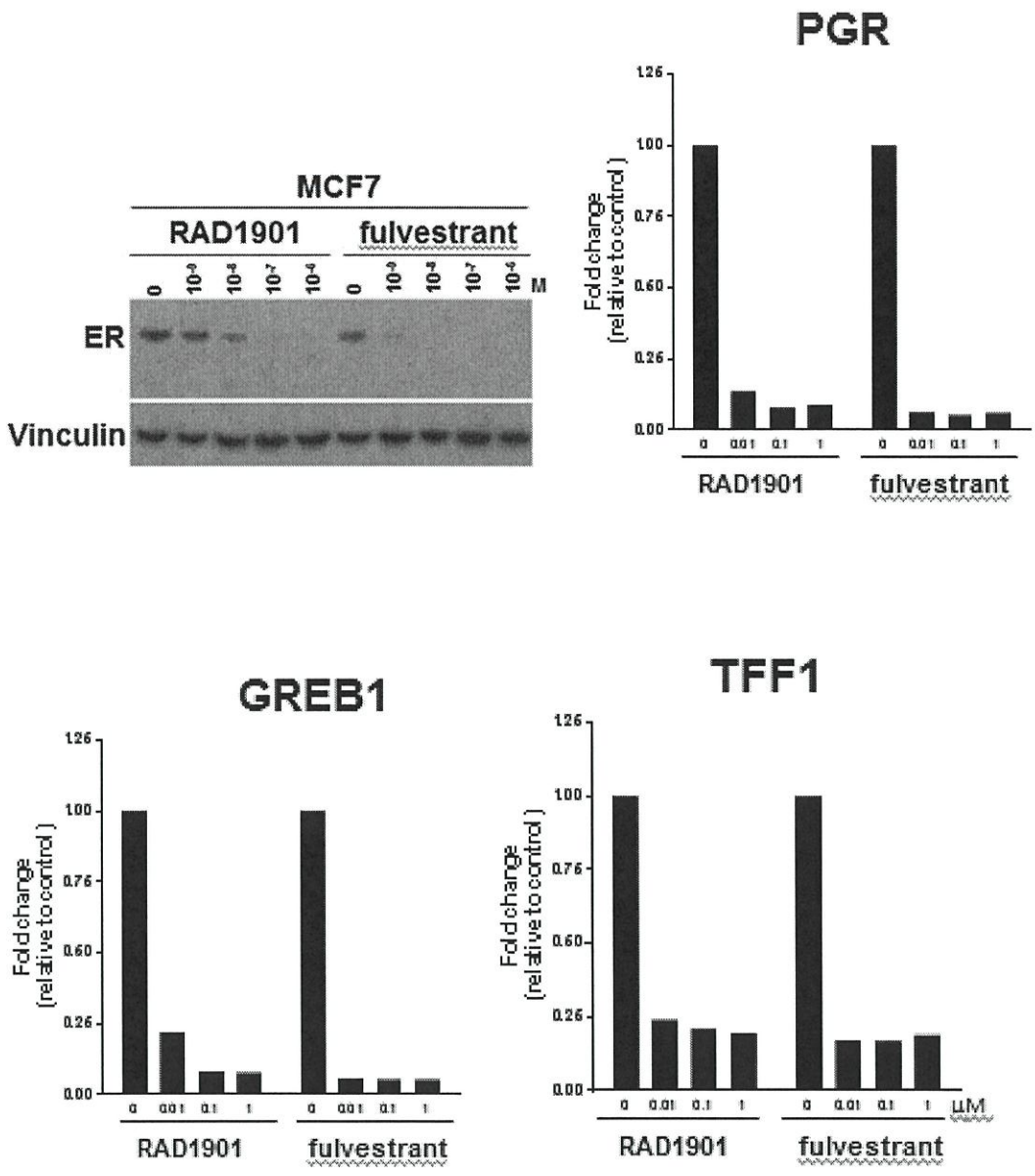

MCF7
RAD1901
fulvestrant
0
10-9
10-8
10-7
10-6
M
ER
Vinculin
PGR
Fold change (relative to control)
1.26
1.00
0.76
0.60
0.26
0.00
0
0.01
0.1
1
RAD1901
fulvestrant
GREB1
TFF1
µM

Fig. 17B

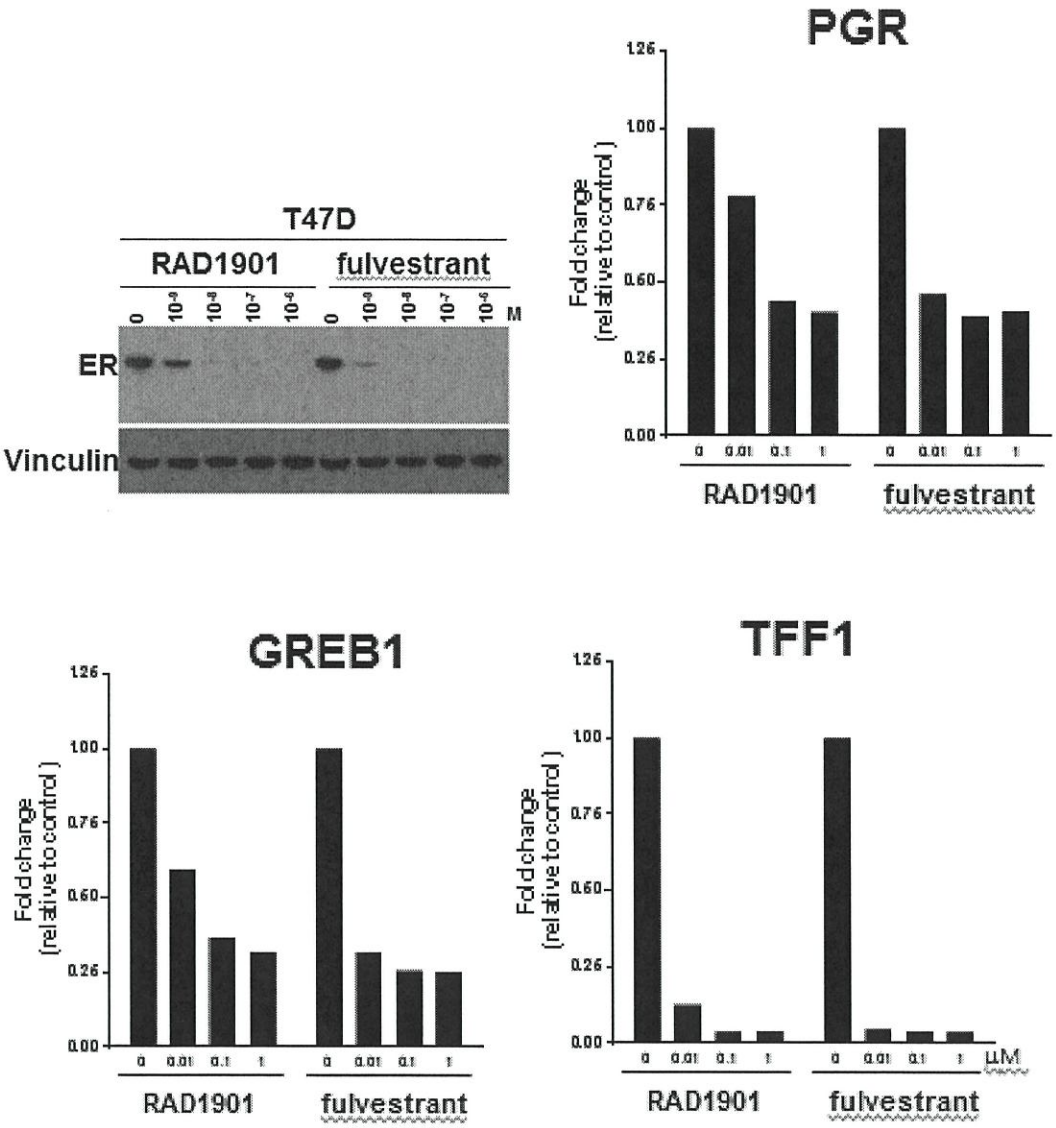

T47D
RAD1901
fulvestrant
0
10-9
10-8
10-7
10-6
M
ER
Vinculin
PGR
Fold change (relative to control)
1.26
1.00
0.76
0.60
0.26
0.00
0
0.01
0.1
1
RAD1901
fulvestrant
GREB1
TFF1
μM

Fig. 27

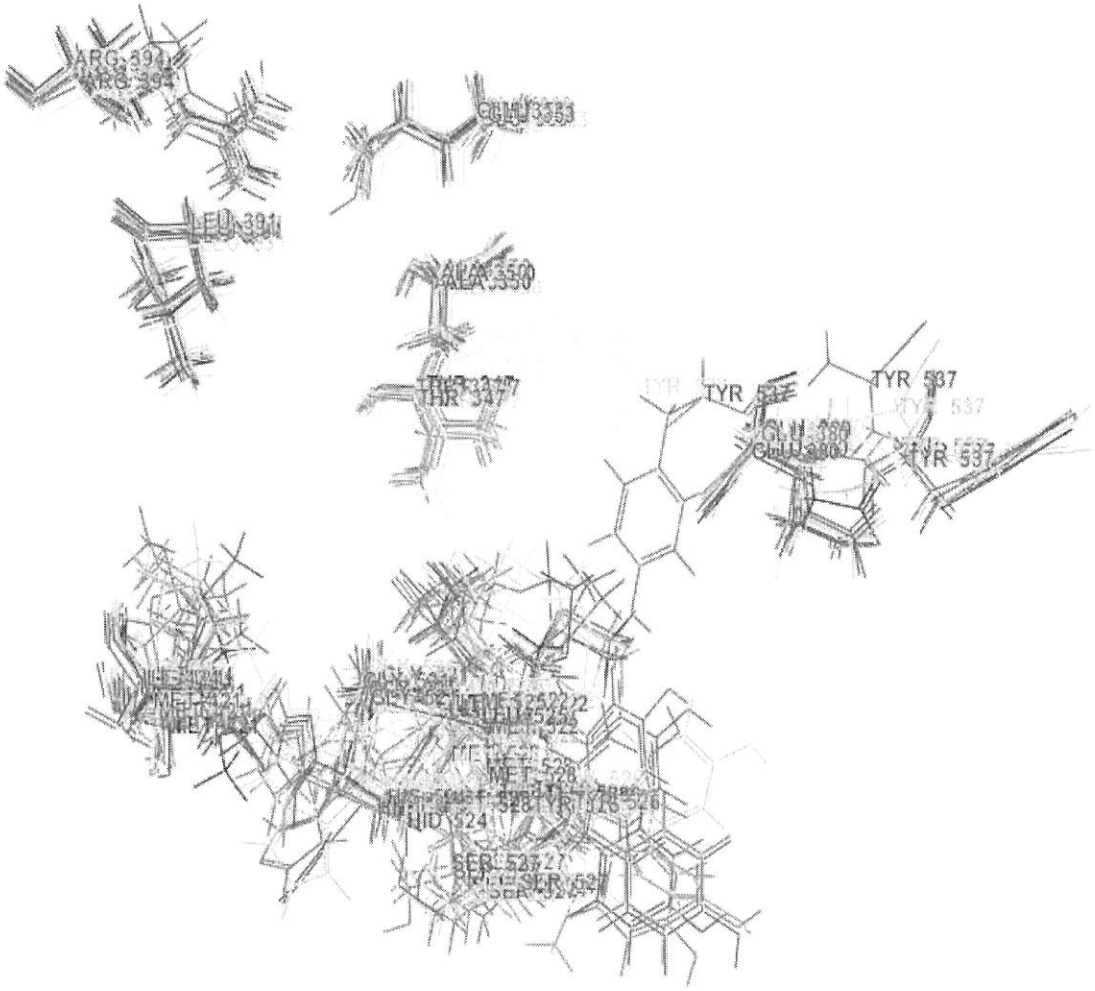

ARG 394
GLU 353
LEU 391
ALA 350
THR 347
TYR 537
TYR 537
GLU 380
TYR 537
MET 528
HID 524
SER 527

Fig. 28A

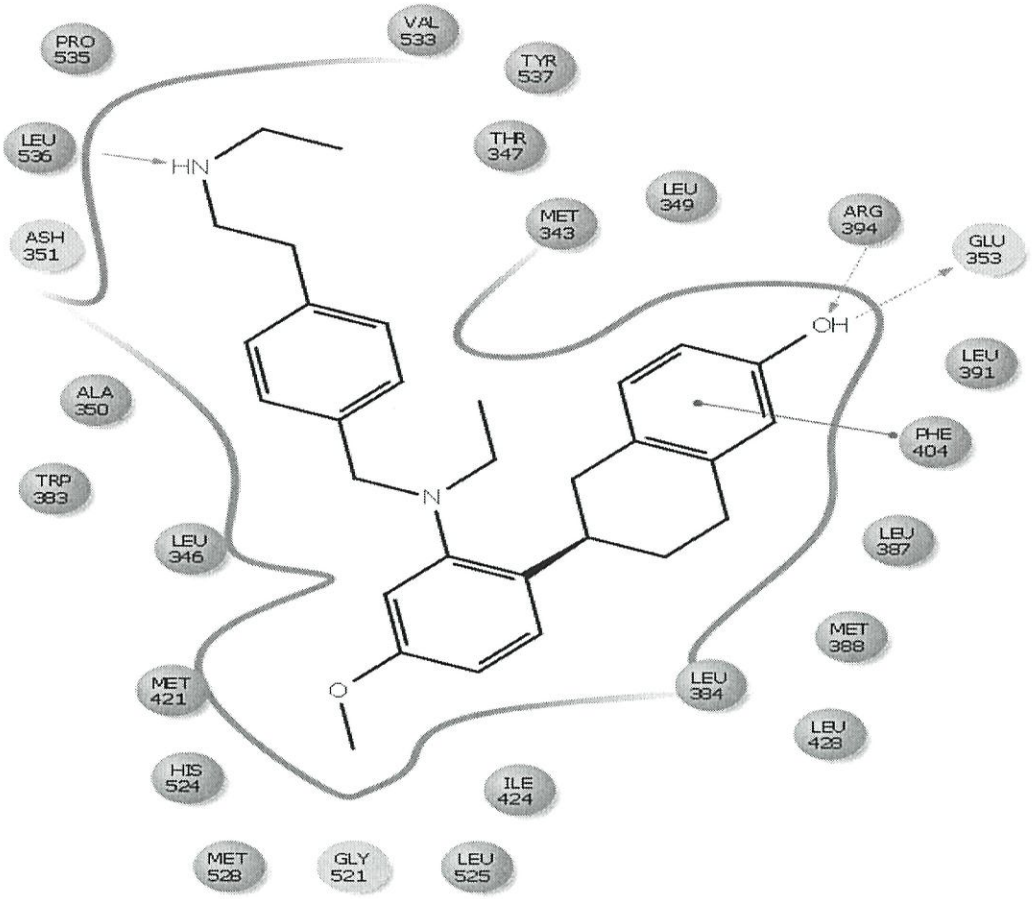

PRO 535
VAL 533
TYR 537
LEU 536
HN
THR 347
LEU 349
MET 343
ARG 394
GLU 353
ASH 351
OH
LEU 391
ALA 350
PHE 404
TRP 383
N
LEU 346
LEU 387
MET 388
MET 421
O
LEU 384
LEU 428
HIS 524
ILE 424
MET 528
GLY 521
LEU 525

Fig. 28B

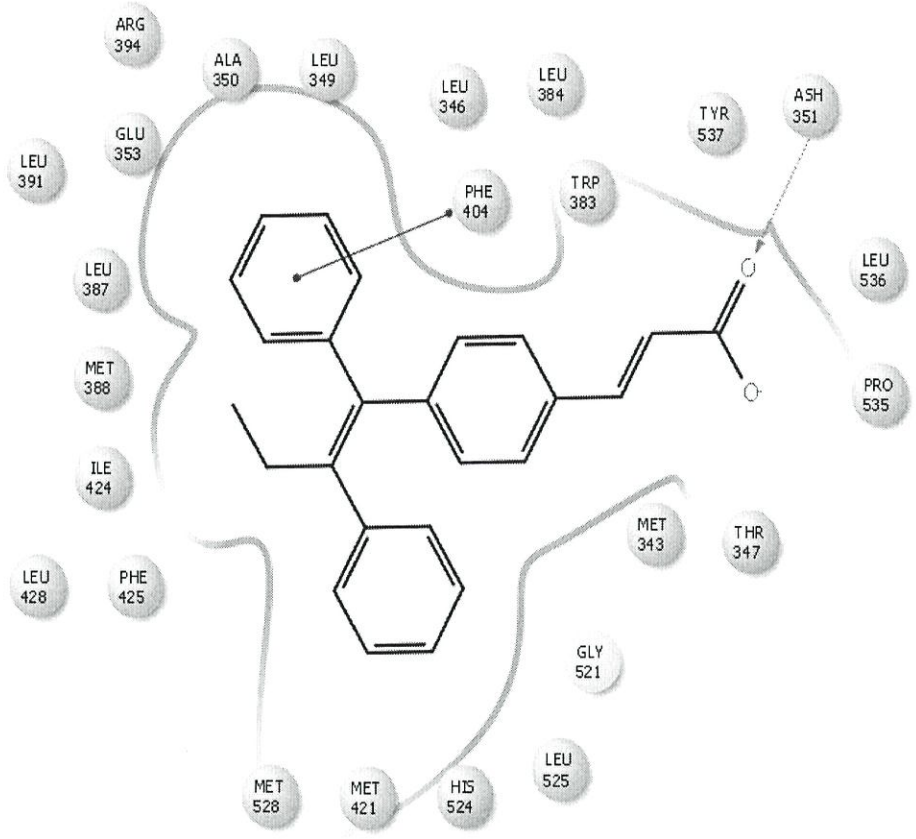

ARG 394
ALA 350
LEU 349
LEU 346
LEU 384
TYR 537
ASH 351
GLU 353
LEU 391
PHE 404
TRP 383
LEU 536
LEU 387
MET 388
PRO 535
ILE 424
MET 343
THR 347
LEU 428
PHE 425
GLY 521
LEU 525
MET 528
MET 421
HIS 524

Fig. 29A

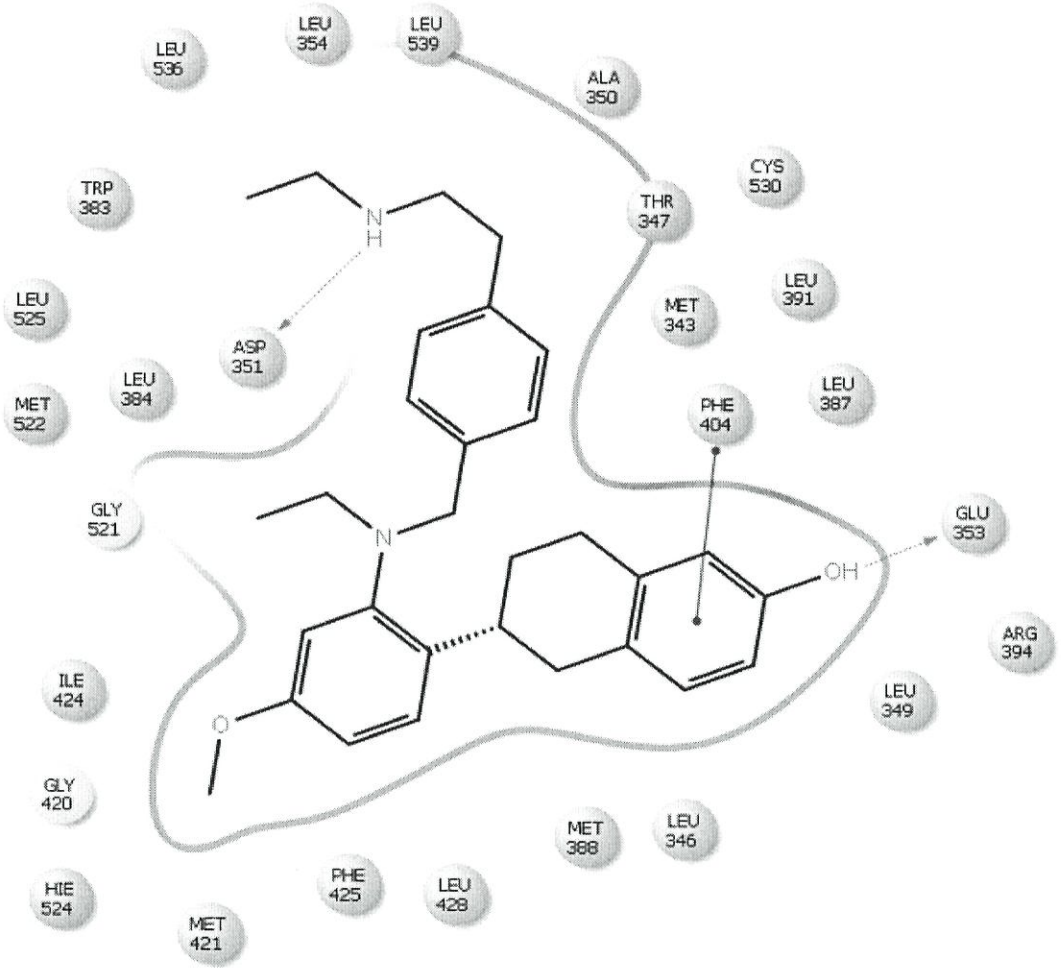

LEU 354
LEU 539
LEU 536
ALA 350
CYS 530
TRP 383
THR 347
N
H
LEU 391
LEU 525
MET 343
ASP 351
LEU 384
LEU 387
MET 522
PHE 404
GLY 521
N
GLU 353
OH
ARG 394
ILE 424
LEU 349
O
GLY 420
MET 388
LEU 346
PHE 425
LEU 428
HIE 524
MET 421

Fig. 29B

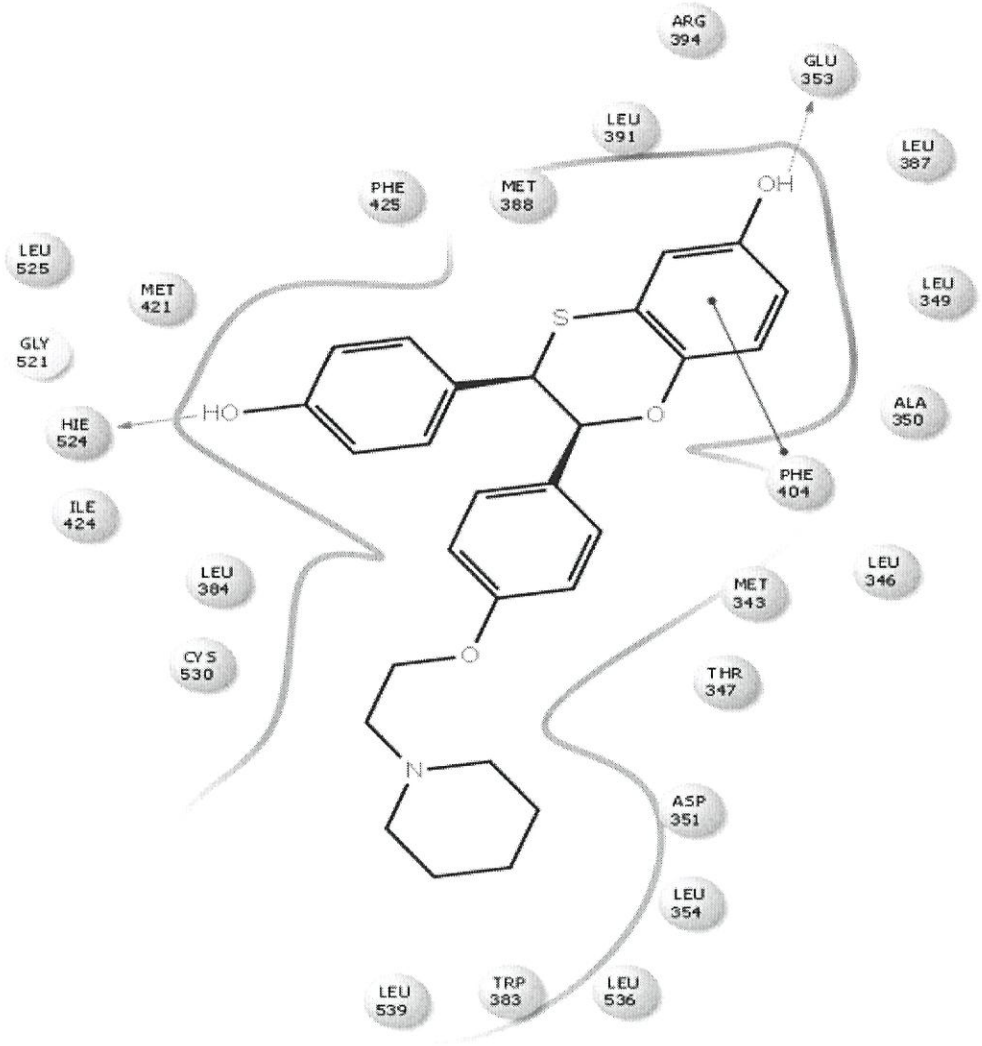

ARG 394
GLU 353
LEU 391
LEU 387
PHE 425
MET 388
OH
LEU 525
MET 421
LEU 349
GLY 521
S
HO
HIE 524
O
ALA 350
PHE 404
ILE 424
LEU 384
LEU 346
MET 343
CYS 530
O
THR 347
N
ASP 351
LEU 354
LEU 539
TRP 383
LEU 536

Fig. 30A

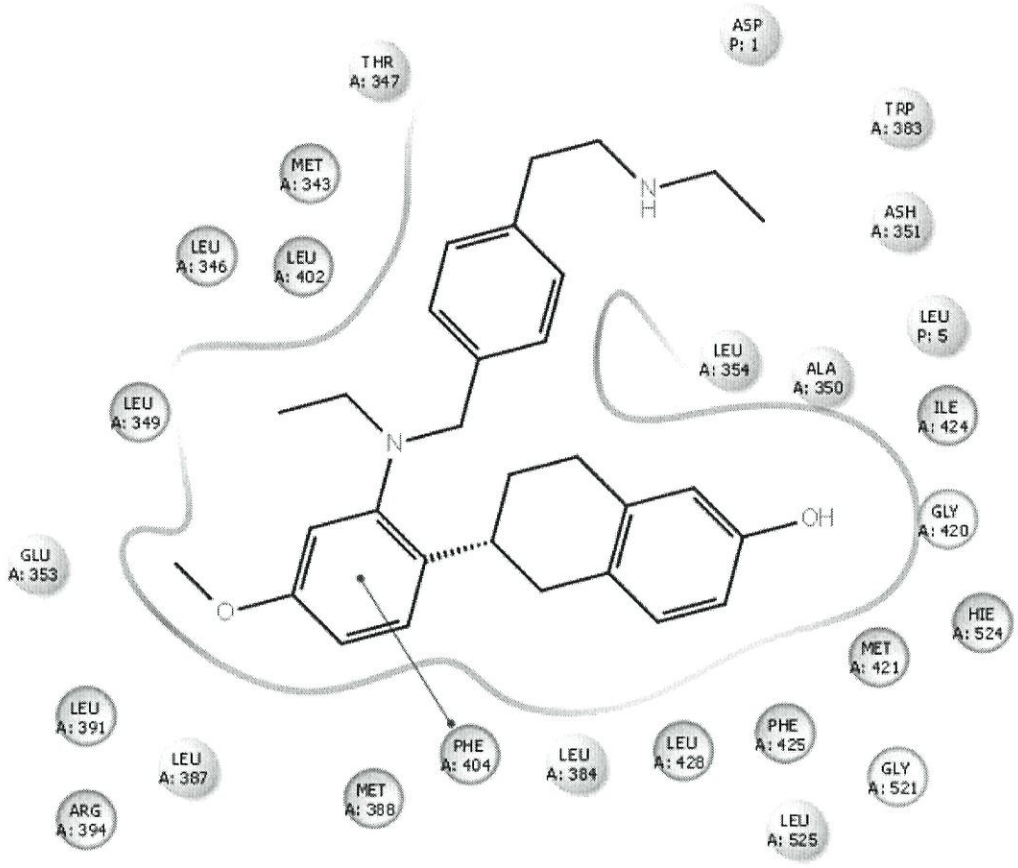

ASP
P: 1
THR
A: 347
TRP
A: 383
MET
A: 343
ASH
A: 351
LEU
A: 346
LEU
A: 402
LEU
P: 5
LEU
A: 354
ALA
A: 350
LEU
A: 349
ILE
A: 424
N
OH
GLY
A: 420
GLU
A: 353
O
HIE
A: 524
MET
A: 421
LEU
A: 391
PHE
A: 425
PHE
A: 404
LEU
A: 384
LEU
A: 428
LEU
A: 387
GLY
A: 521
MET
A: 388
ARG
A: 394
LEU
A: 525

Fig. 30B

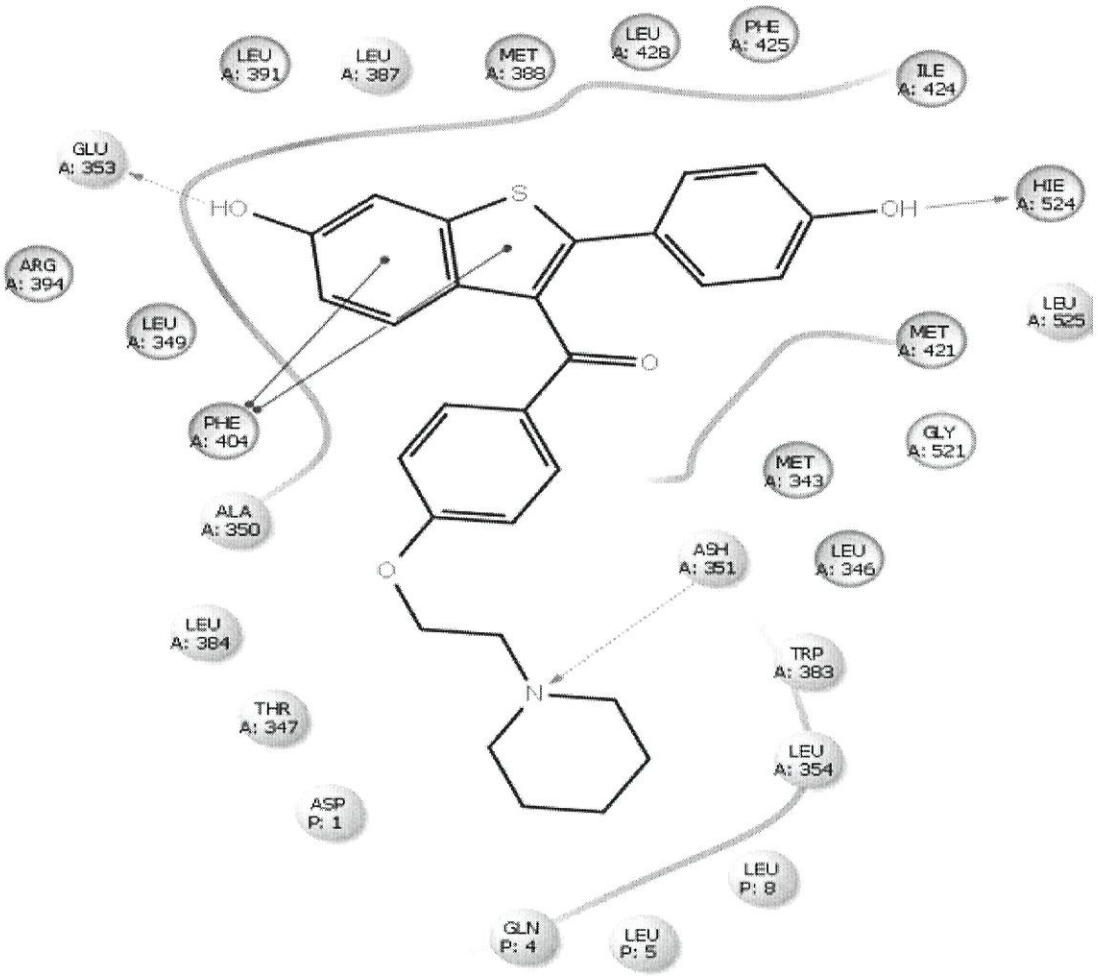

LEU A: 391
LEU A: 387
MET A: 388
LEU A: 428
PHE A: 425
ILE A: 424
GLU A: 353
HO
S
OH
HIE A: 524
ARG A: 394
LEU A: 349
LEU A: 525
MET A: 421
O
PHE A: 404
GLY A: 521
MET A: 343
ALA A: 350
ASH A: 351
LEU A: 346
O
LEU A: 384
TRP A: 383
N
THR A: 347
LEU A: 354
ASP P: 1
LEU P: 8
GLN P: 4
LEU P: 5

Fig. 31A

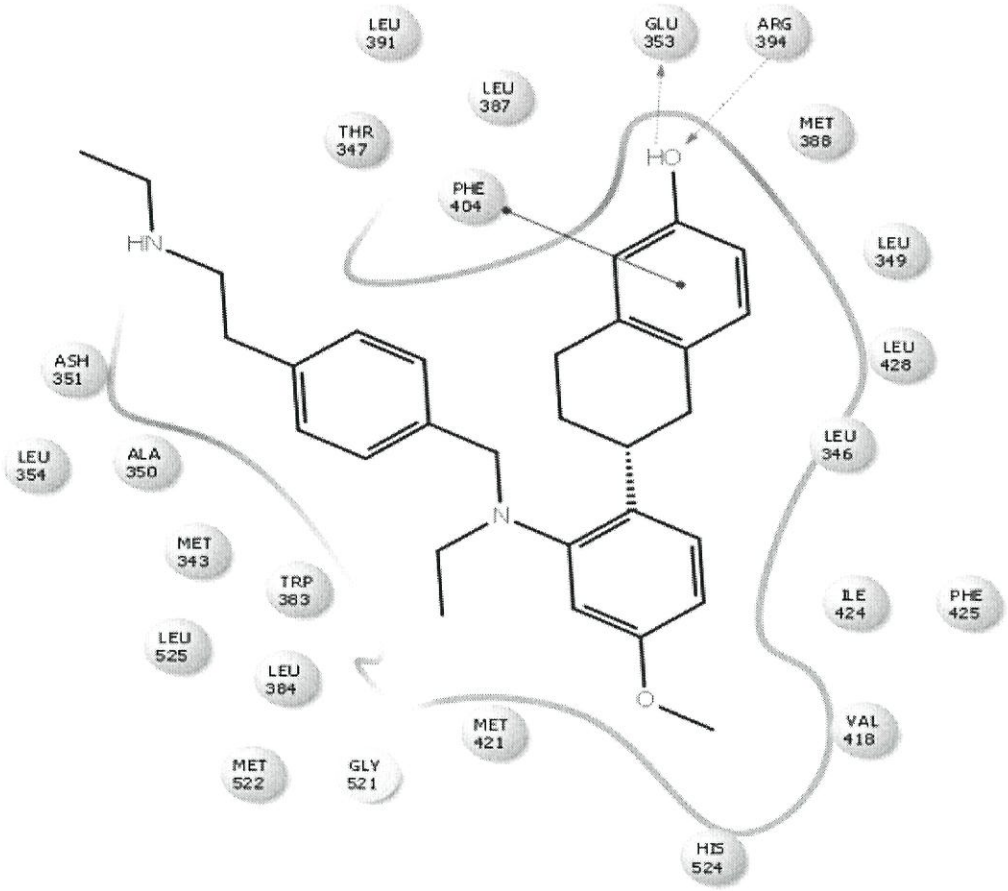

LEU 391
GLU 353
ARG 394
LEU 387
MET 388
THR 347
HO
PHE 404
HN
LEU 349
LEU 428
ASH 351
LEU 346
LEU 354
ALA 350
N
MET 343
TRP 383
ILE 424
PHE 425
LEU 525
LEU 384
O
MET 421
VAL 418
MET 522
GLY 521
HIS 524

Fig. 31B

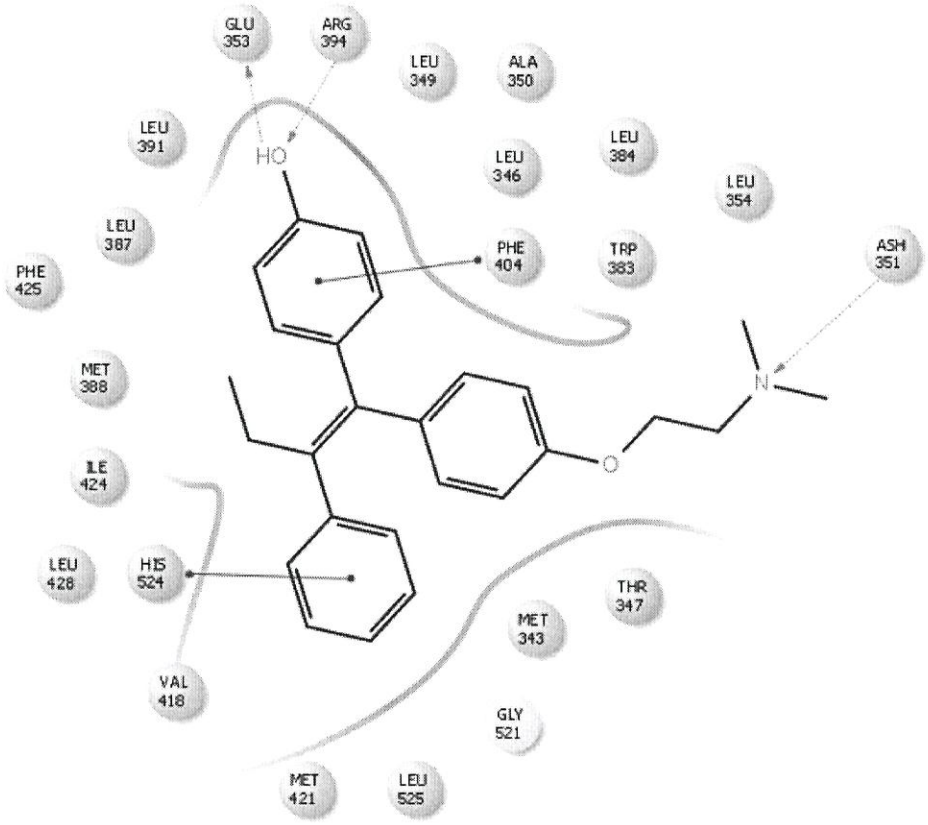

GLU 353
ARG 394
LEU 349
ALA 350
LEU 391
HO
LEU 346
LEU 384
LEU 354
LEU 387
PHE 404
TRP 383
ASH 351
PHE 425
MET 388
N
O
ILE 424
LEU 428
HIS 524
THR 347
MET 343
VAL 418
GLY 521
MET 421
LEU 525

Fig. 32A

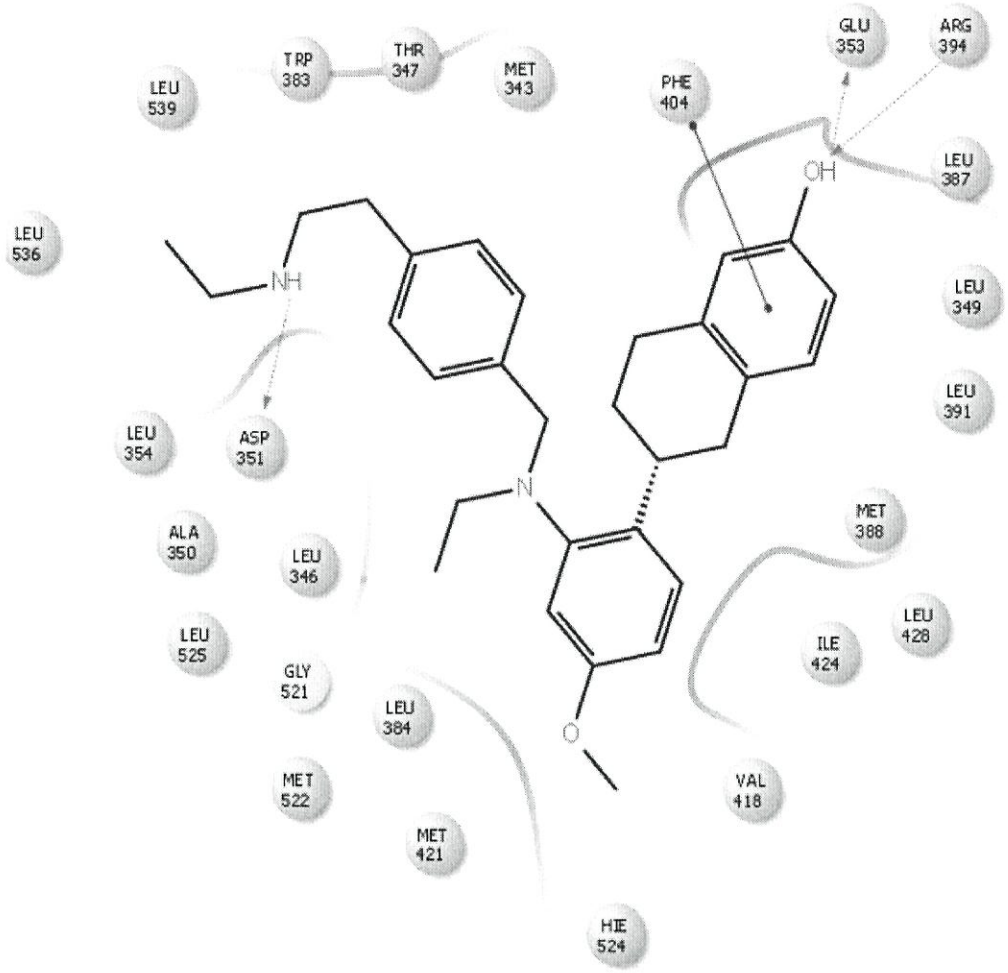

GLU 353
ARG 394
TRP 383
THR 347
MET 343
PHE 404
LEU 539
LEU 387
OH
LEU 536
NH
LEU 349
LEU 391
LEU 354
ASP 351
N
MET 388
ALA 350
LEU 346
LEU 428
LEU 525
ILE 424
GLY 521
LEU 384
O
MET 522
VAL 418
MET 421
HIE 524

Fig. 32B

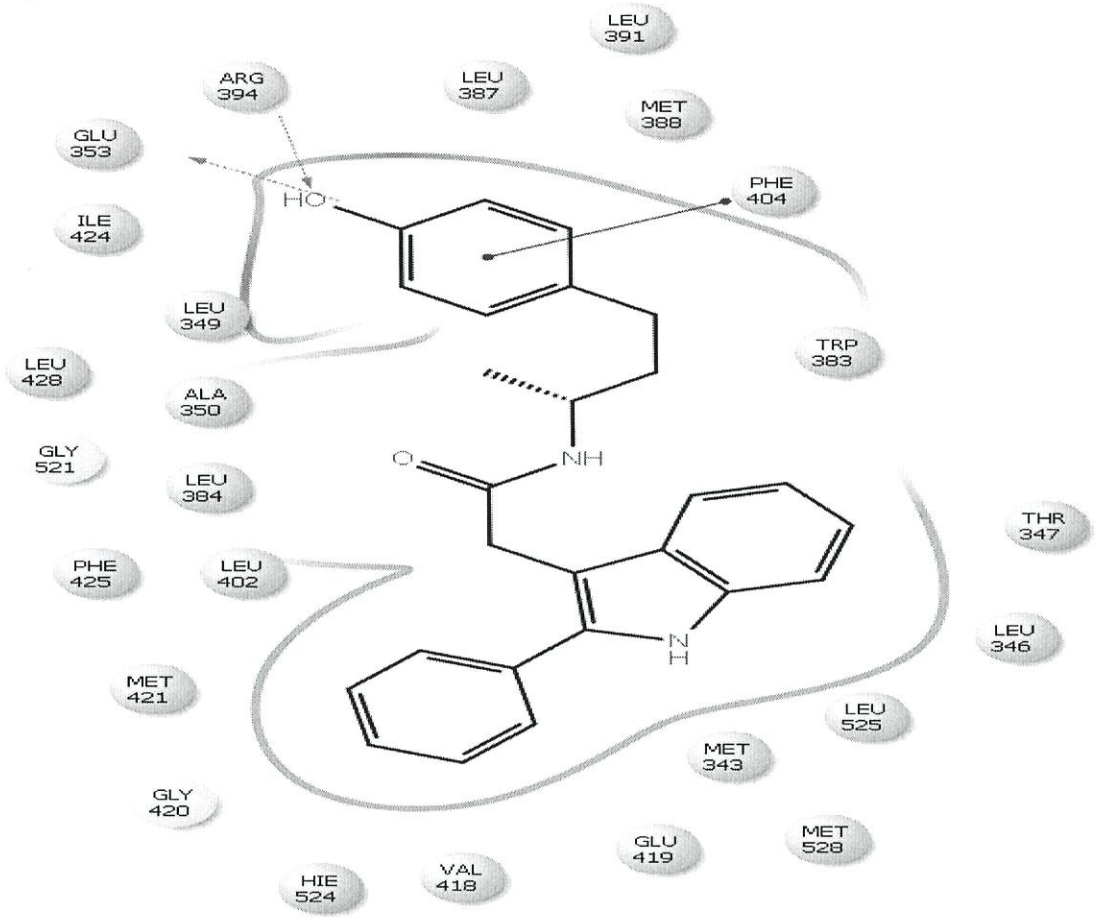

LEU 391
ARG 394
LEU 387
MET 388
GLU 353
PHE 404
HO
ILE 424
LEU 349
TRP 383
LEU 428
ALA 350
GLY 521
O
NH
LEU 384
THR 347
PHE 425
LEU 402
N H
LEU 346
MET 421
LEU 525
MET 343
GLY 420
GLU 419
MET 528
HIE 524
VAL 418

Fig. 36A

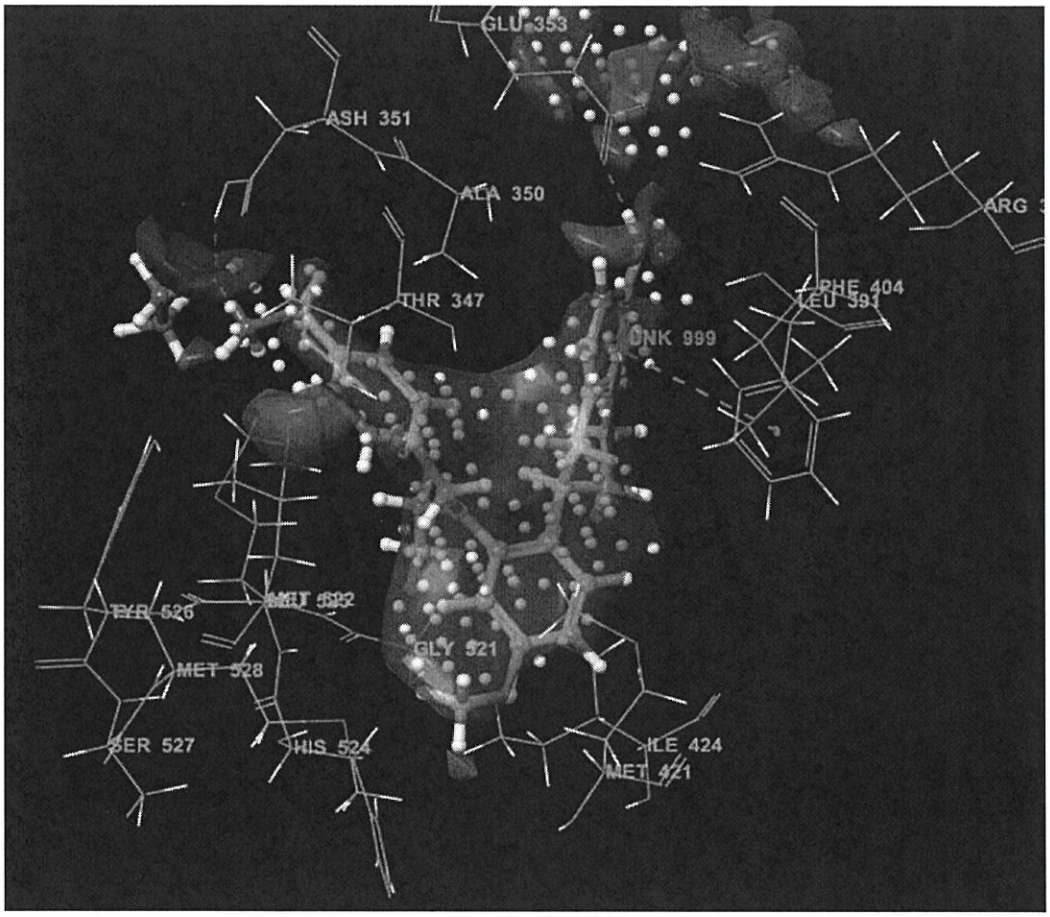

GLU 353
ASH 351
ALA 350
THR 347
UNK 999
PHE 404
LEU 391
TYR 526
GLY 521
MET 528
SER 527
HIS 524
ILE 424

Fig. 36B

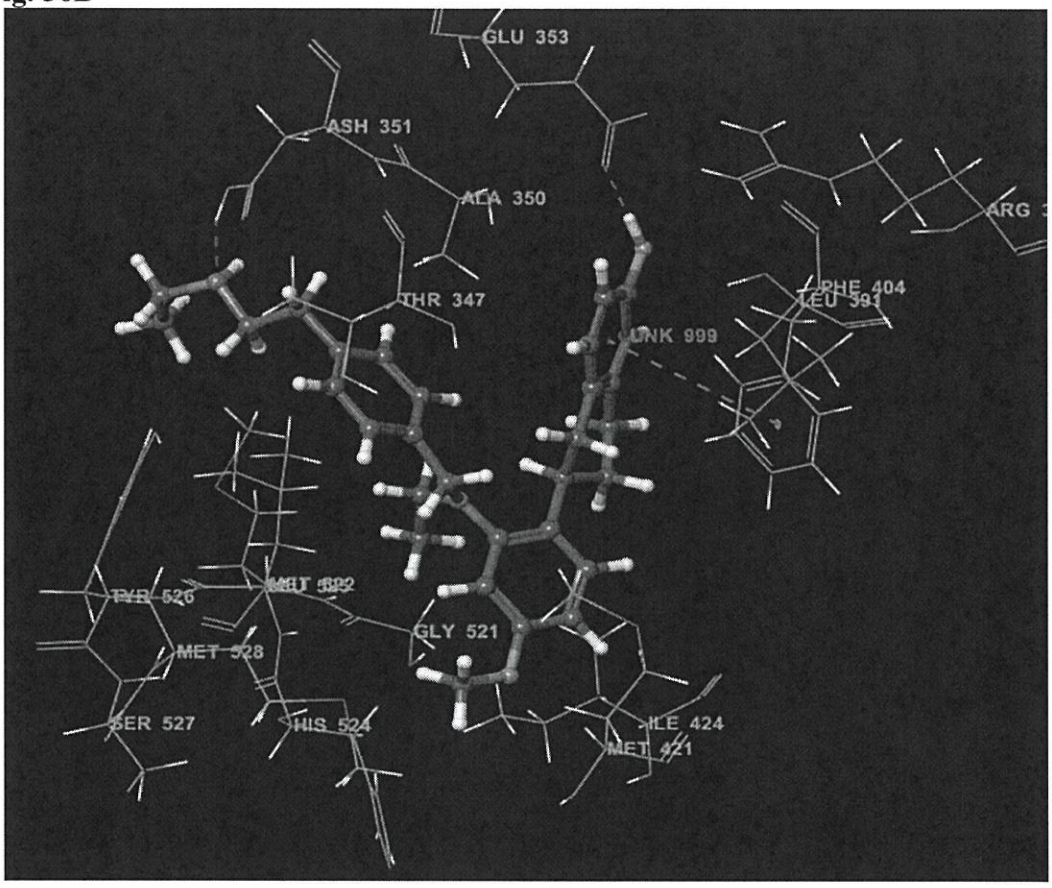
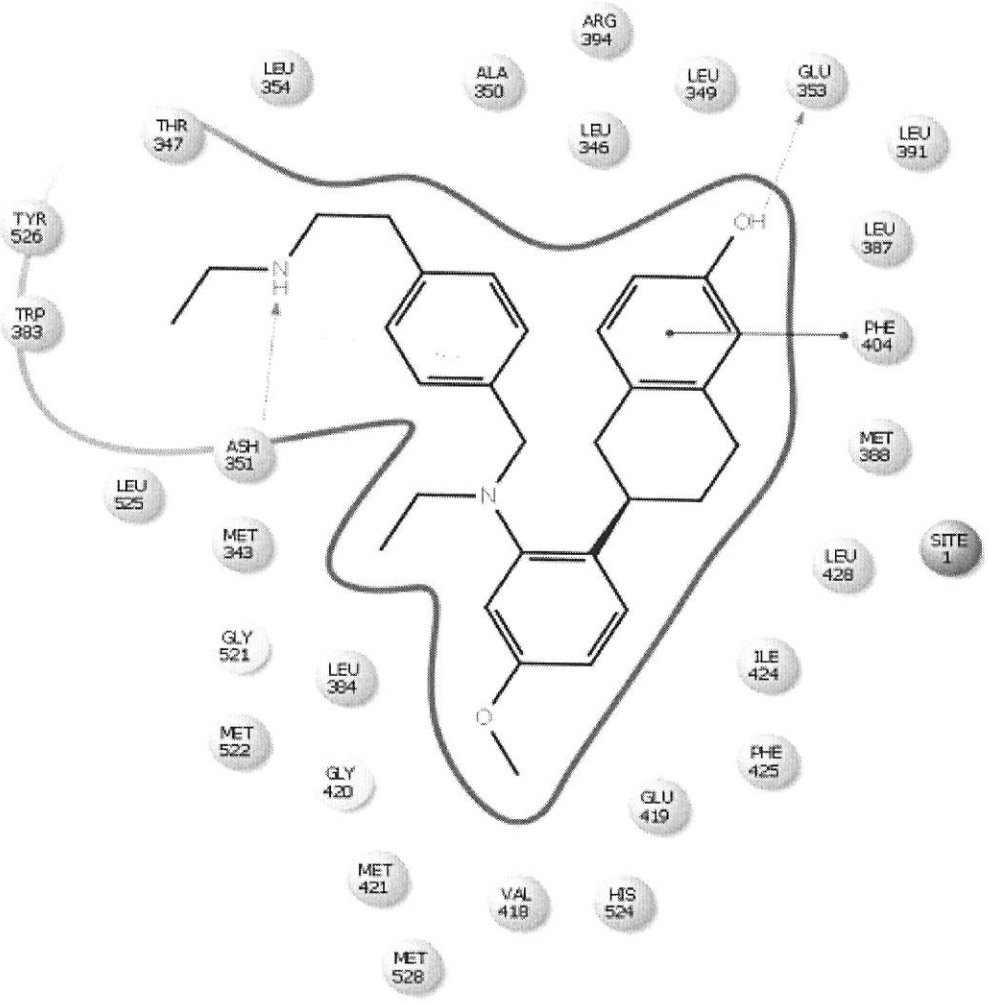

GLU 353
ASH 351
ALA 350
THR 347
UNK 999
PHE 404
LEU 391
TYR 526
GLY 521
MET 528
SER 527
HIS 524
ILE 424
MET 421

Fig. 36C


ARG 394
LEU 354
ALA 350
LEU 349
GLU 353
THR 347
LEU 346
LEU 391
TYR 526
OH
LEU 387
N
H
TRP 383
PHE 404
ASH 351
MET 388
LEU 525
N
MET 343
SITE 1
LEU 428
GLY 521
ILE 424
LEU 384
O
MET 522
PHE 425
GLY 420
GLU 419
MET 421
VAL 418
HIS 524
MET 528