FIG. 1

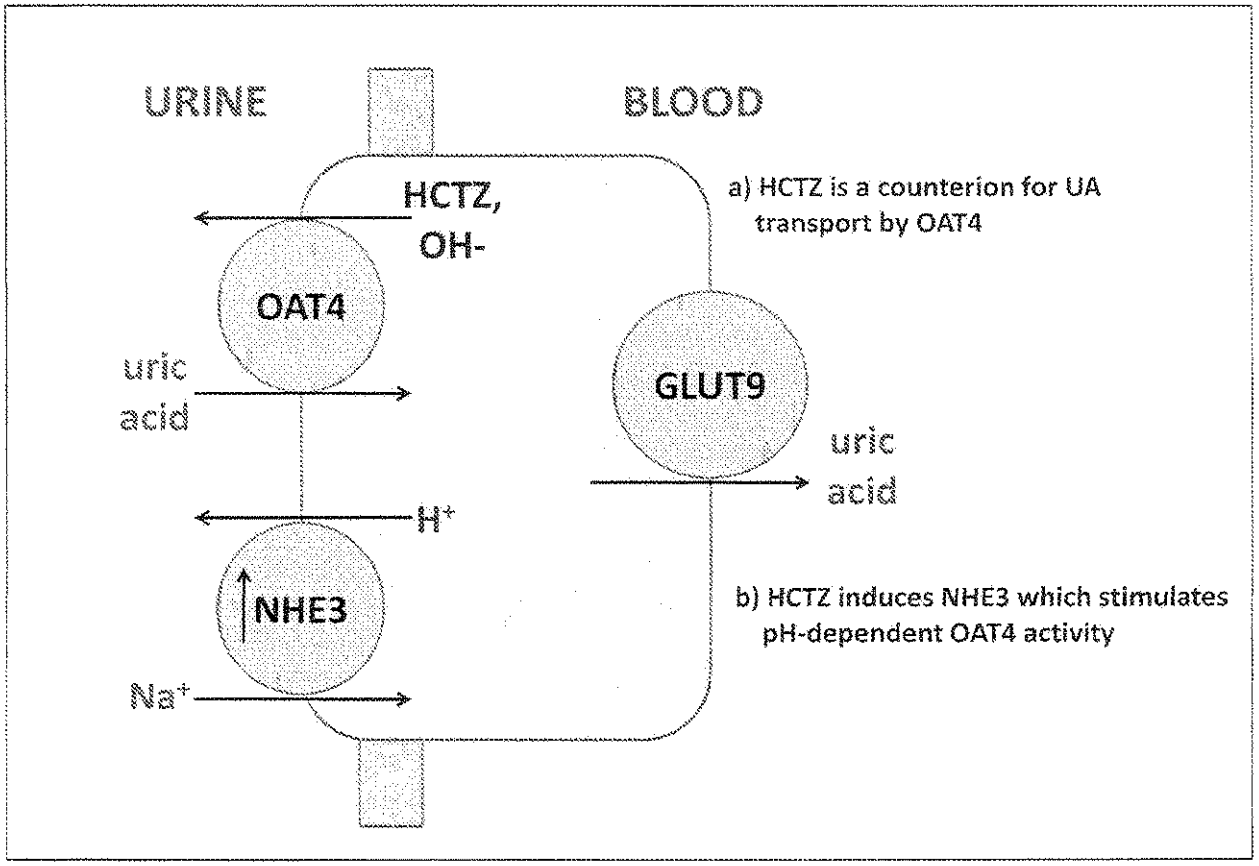

URINE
BLOOD
HCTZ,
OH-
a) HCTZ is a counterion for UA transport by OAT4
OAT4
uric acid
GLUT9
uric acid
H+
NHE3
b) HCTZ induces NHE3 which stimulates pH-dependent OAT4 activity
Na+

FIG. 2

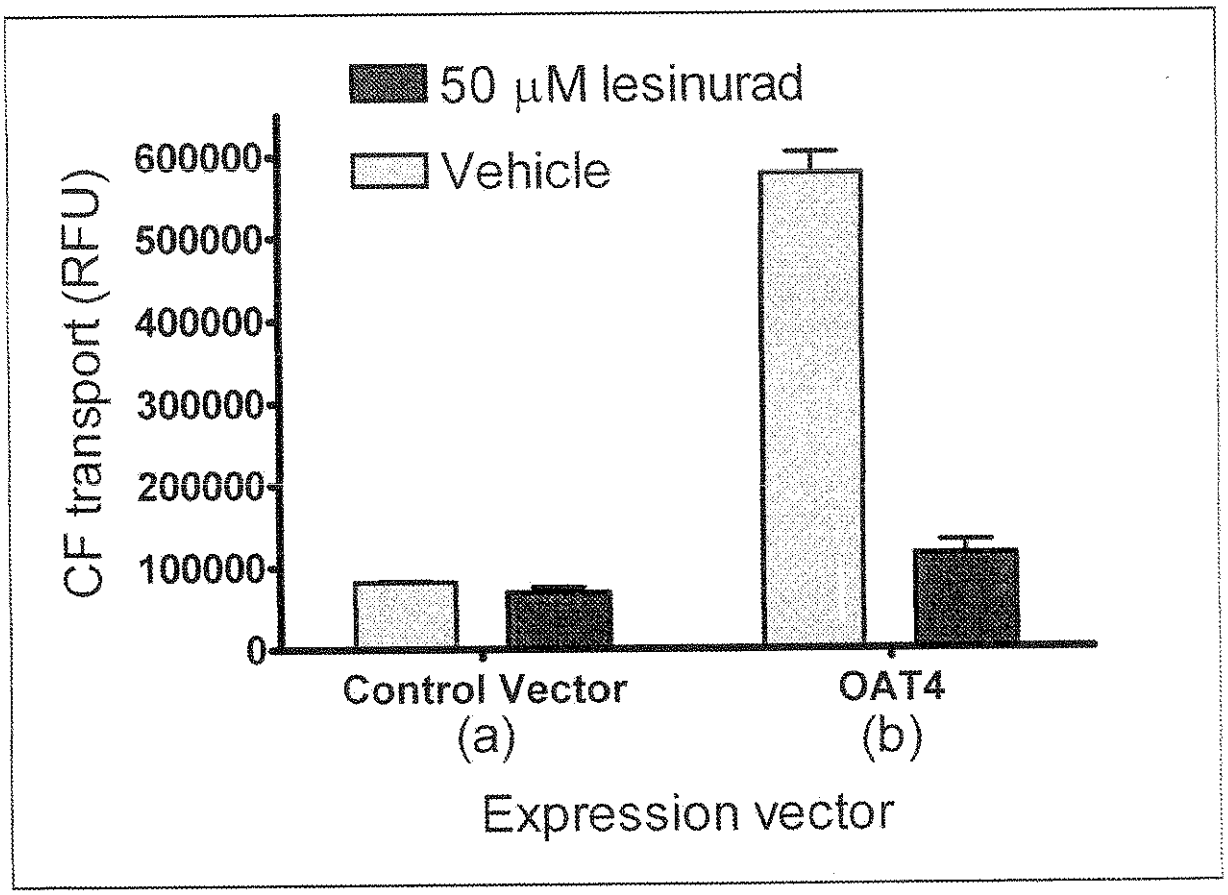

50 μM lesinurad
Vehicle
CF transport (RFU)
600000
500000
400000
300000
200000
100000
0
Control Vector
(a)
OAT4
(b)
Expression vector

FIG. 3

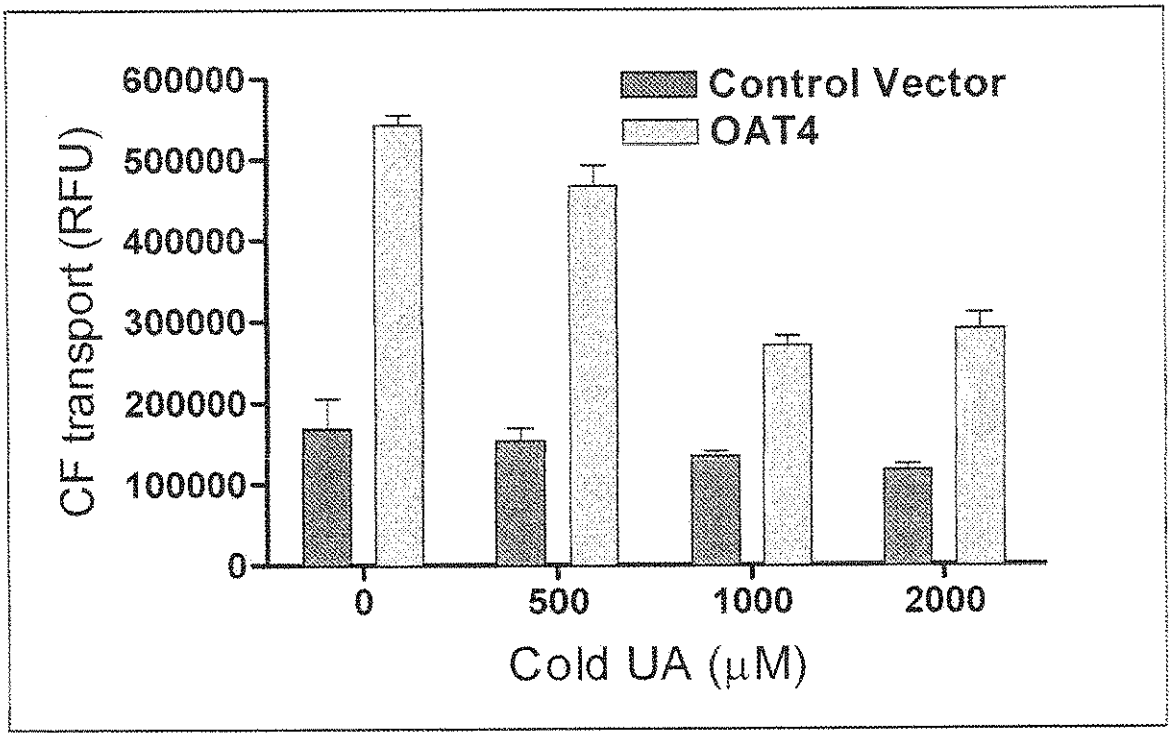

600000
500000
400000
300000
200000
100000
0
CF transport (RFU)
Control Vector
OAT4
0
500
1000
2000
Cold UA (μM)

FIG. 4

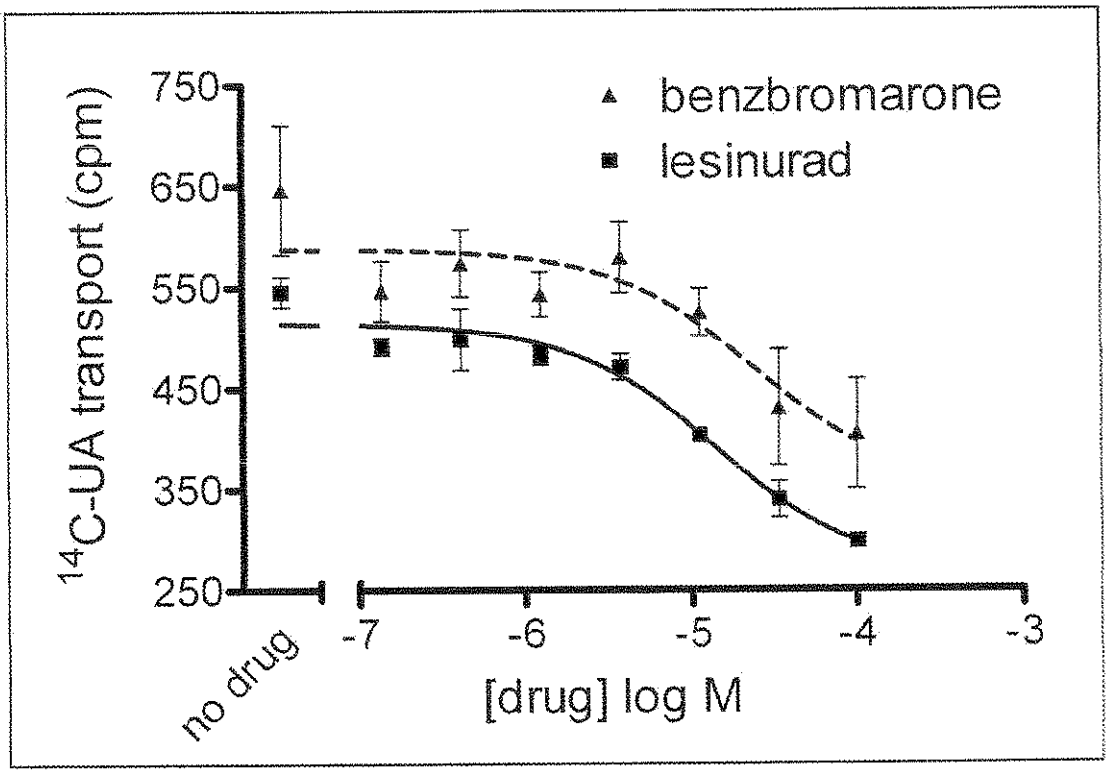

benzbromarone
lesinurad
^{14}C-UA transport (cpm)
750
650
550
450
350
250
no drug
-7
-6
-5
-4
-3
[drug] log M

FIG. 5

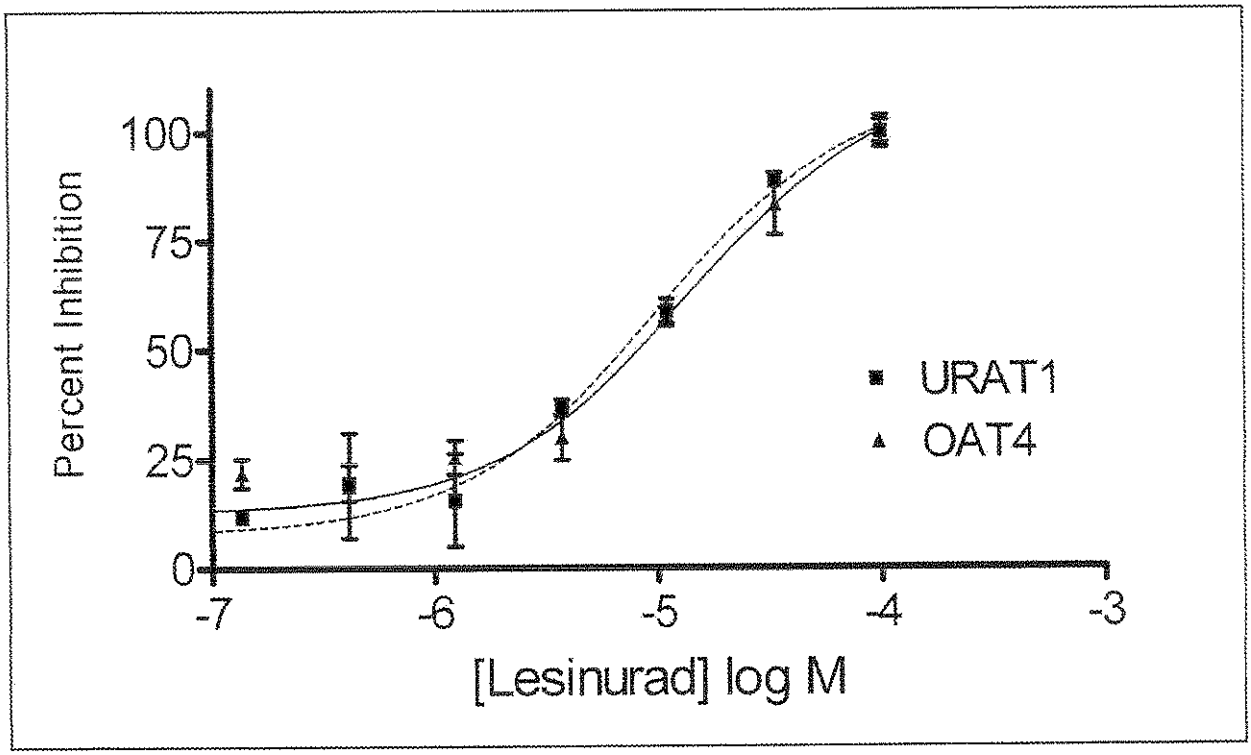

Percent Inhibition
100
75
50
25
0
-7
-6
-5
-4
-3
[Lesinurad] log M
URAT1
OAT4

FIG. 6

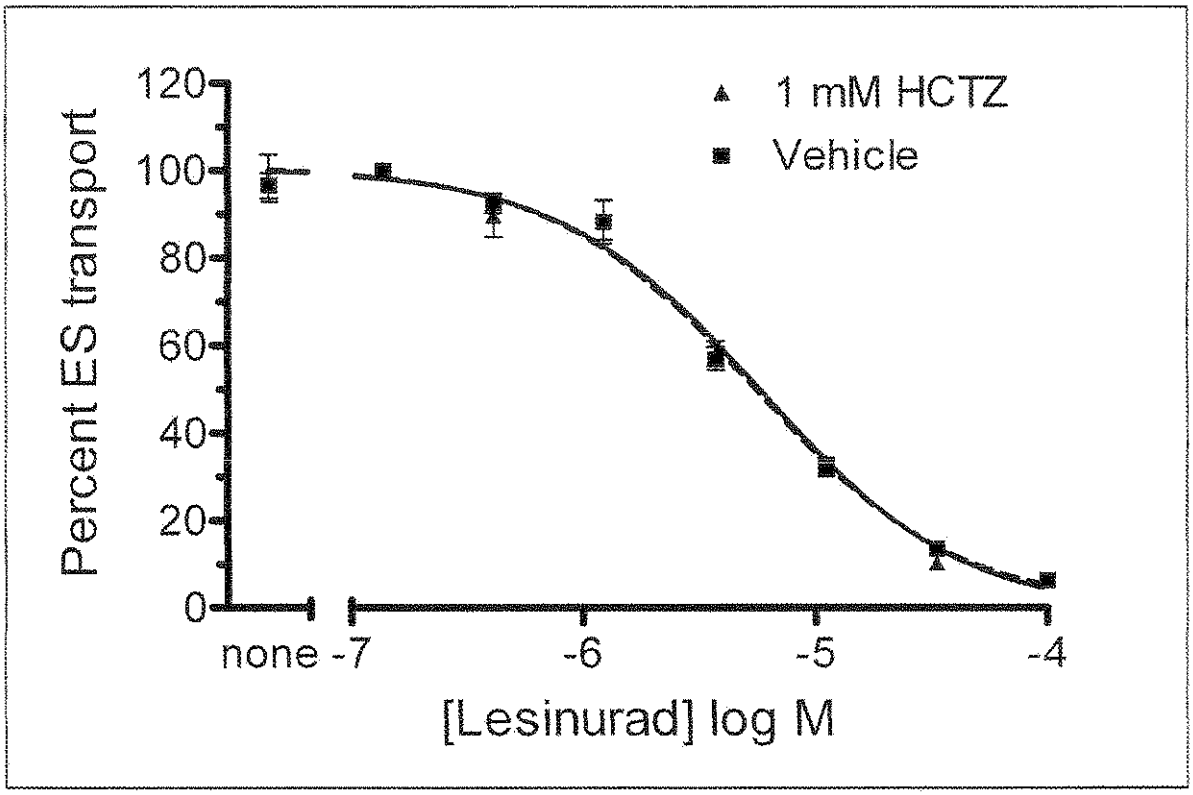
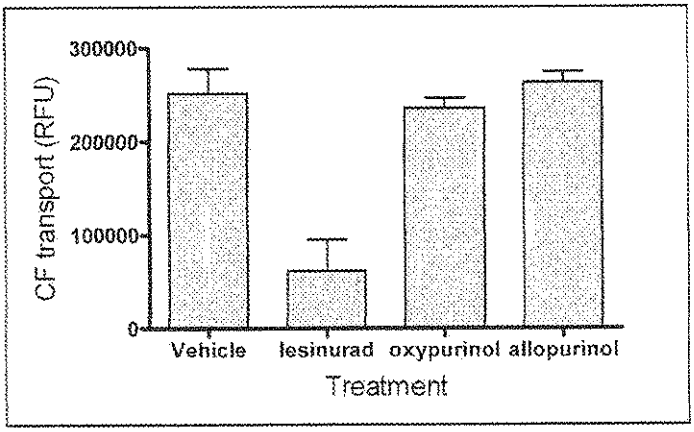
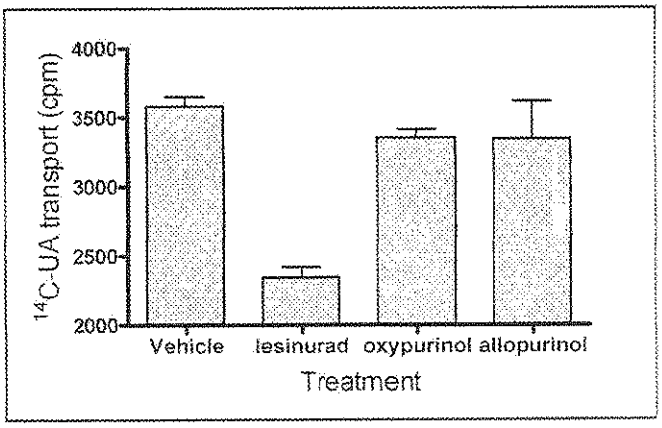

Percent ES transport
120
100
80
60
40
20
0
none
-7
-6
-5
-4
[Lesinurad] log M
1 mM HCTZ
Vehicle

FIG. 7


300000
200000
100000
0
CF transport (RFU)
Vehicle
lesinurad
oxypurinol
allopurinol
Treatment

(a)


4000
3500
3000
2500
2000
14C-UA transport (cpm)
Vehicle
lesinurad
oxypurinol
allopurinol
Treatment

(b)

FIG. 8

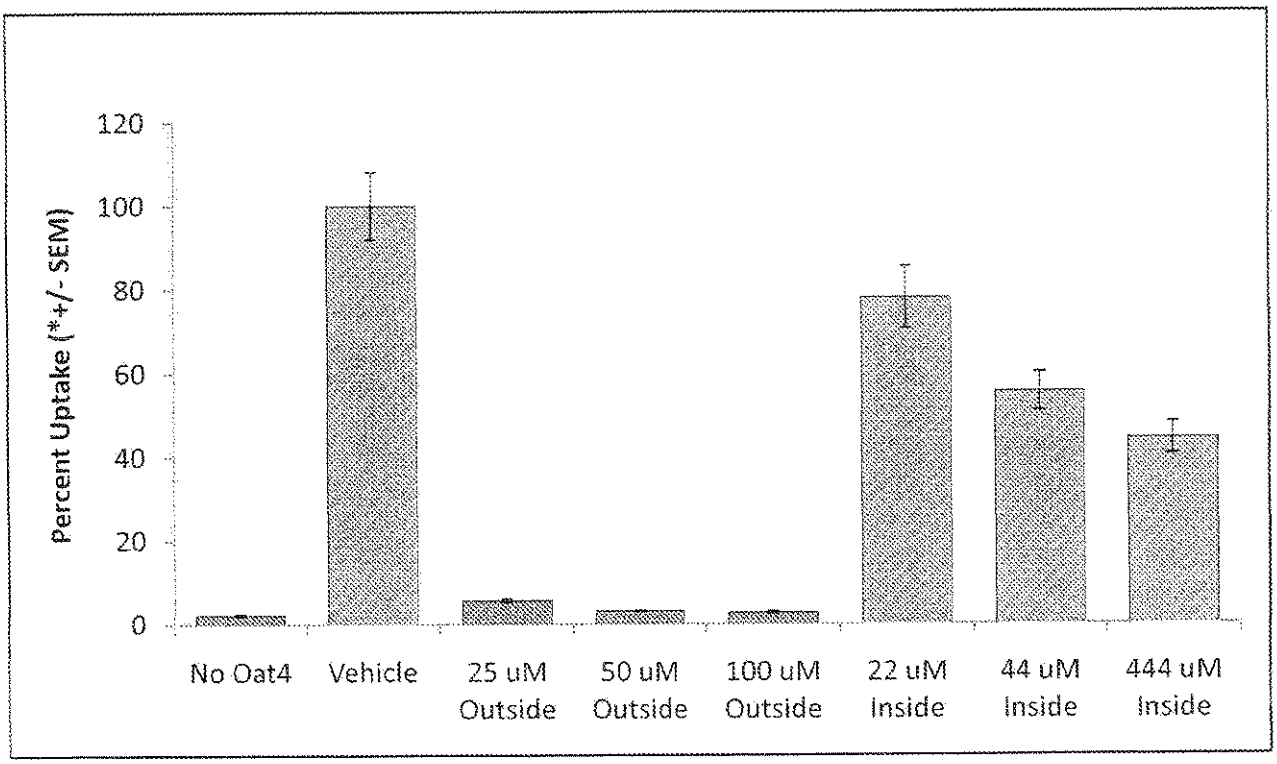

Percent Uptake (*+/- SEM)
120
100
80
60
40
20
0
No Oat4
Vehicle
25 uM Outside
50 uM Outside
100 uM Outside
22 uM Inside
44 uM Inside
444 uM Inside

FIG. 9

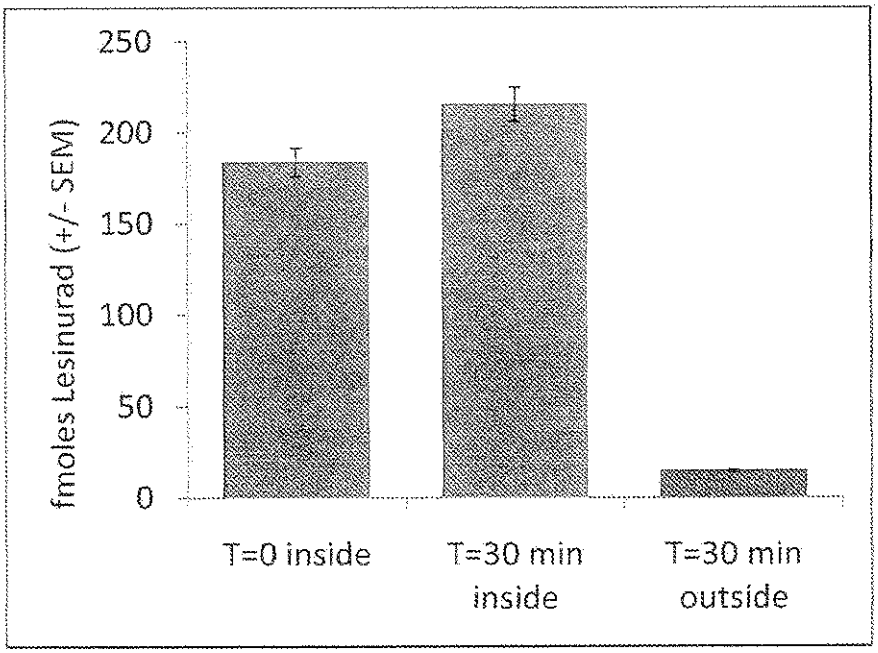

250
200
150
100
50
0
fmoles Lesinurad (+/- SEM)
T=0 inside
T=30 min inside
T=30 min outside

FIG. 10A

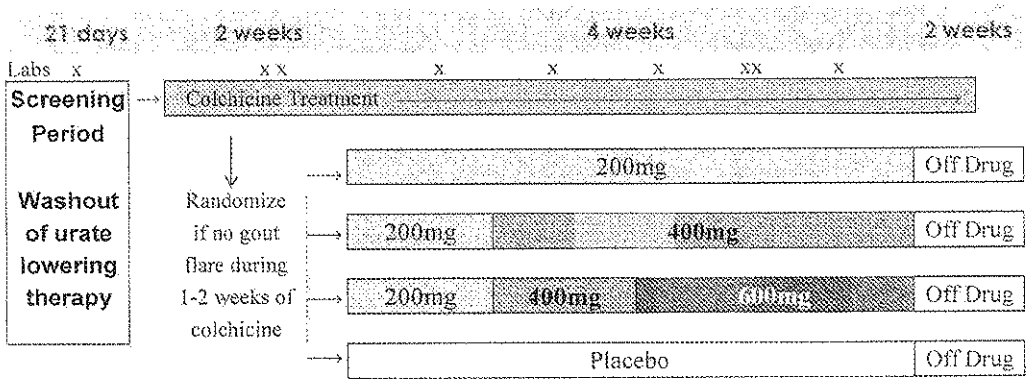


FIG. 10B

