FIG. 1

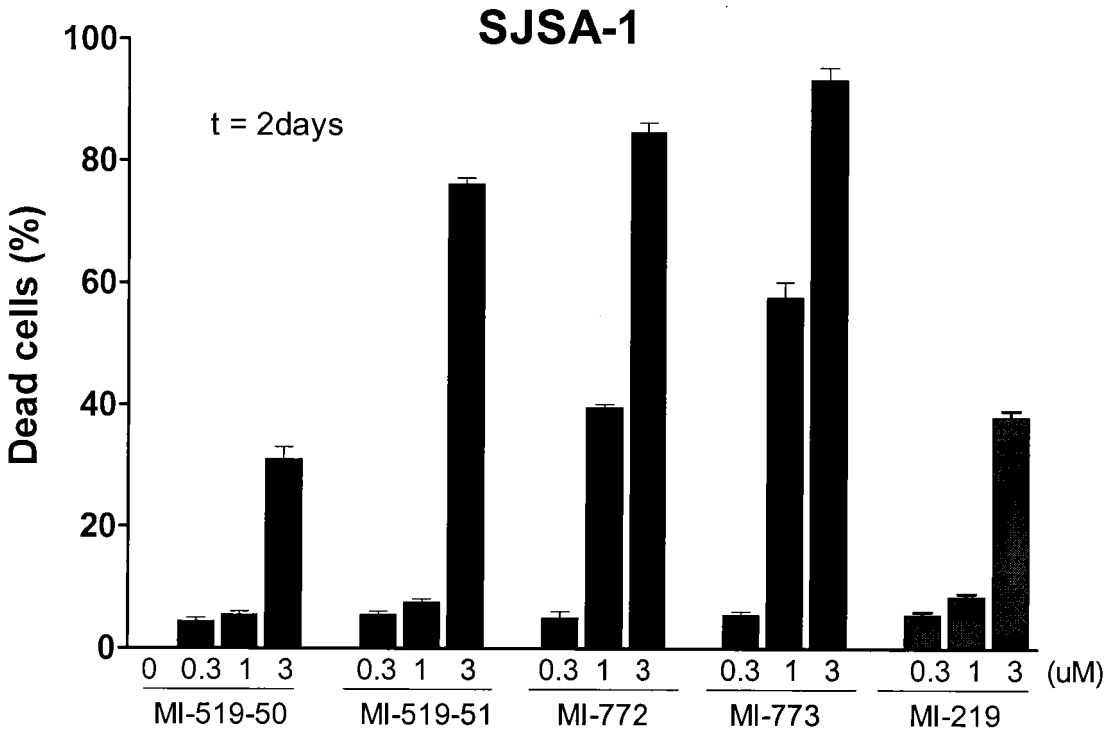

SJSA-1
t = 2days
Dead cells (%)
100
80
60
40
20
0
0 0.3 1 3
0.3 1 3
0.3 1 3
0.3 1 3
0.3 1 3
(uM)
MI-519-50
MI-519-51
MI-772
MI-773
MI-219

FIG. 2

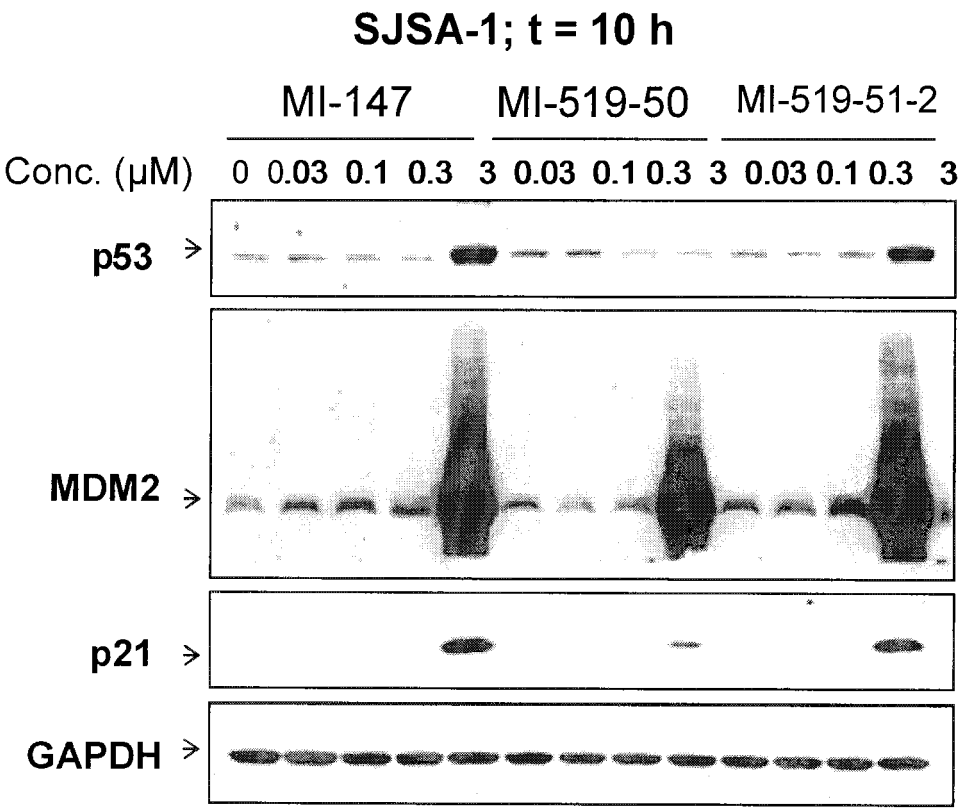

SJSA-1; t = 10 h
MI-147
MI-519-50
MI-519-51-2
Conc. (μM)
0 0.03 0.1 0.3 3 0.03 0.1 0.3 3 0.03 0.1 0.3 3
p53
MDM2
p21
GAPDH

FIG. 3

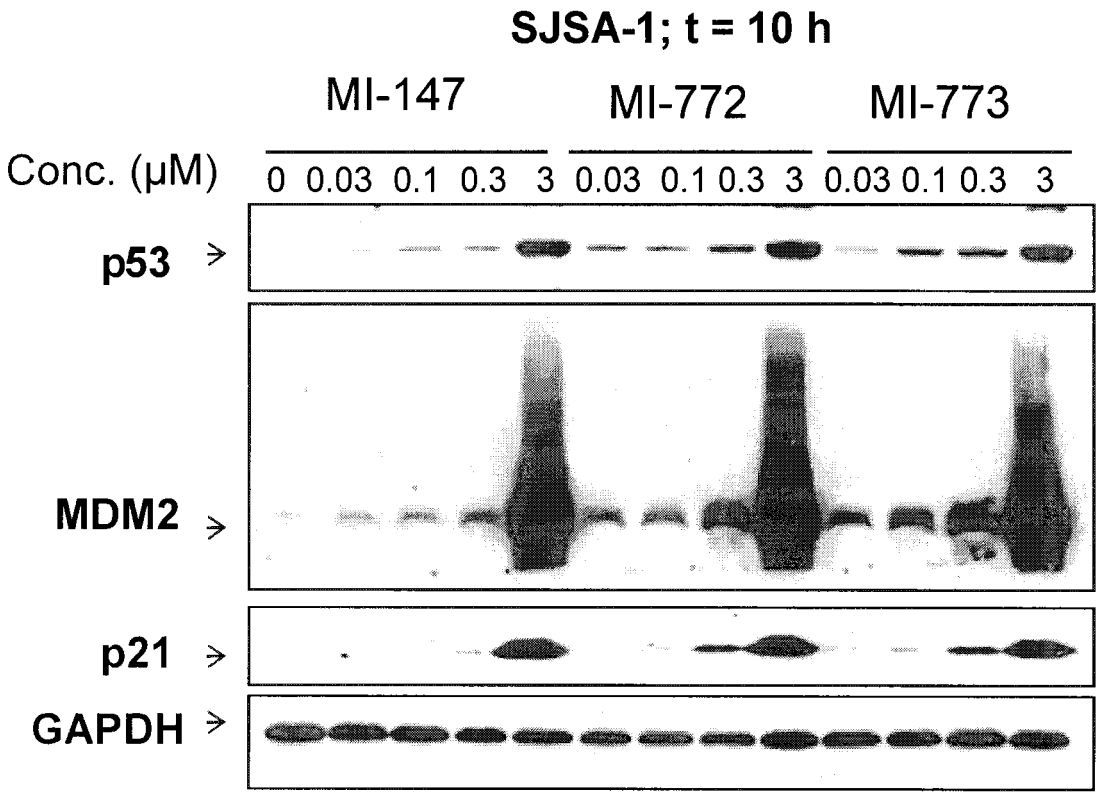

SJSA-1; t = 10 h
MI-147
MI-772
MI-773
Conc. (μM)
0 0.03 0.1 0.3 3 0.03 0.1 0.3 3 0.03 0.1 0.3 3
p53
MDM2
p21
GAPDH

FIG. 4

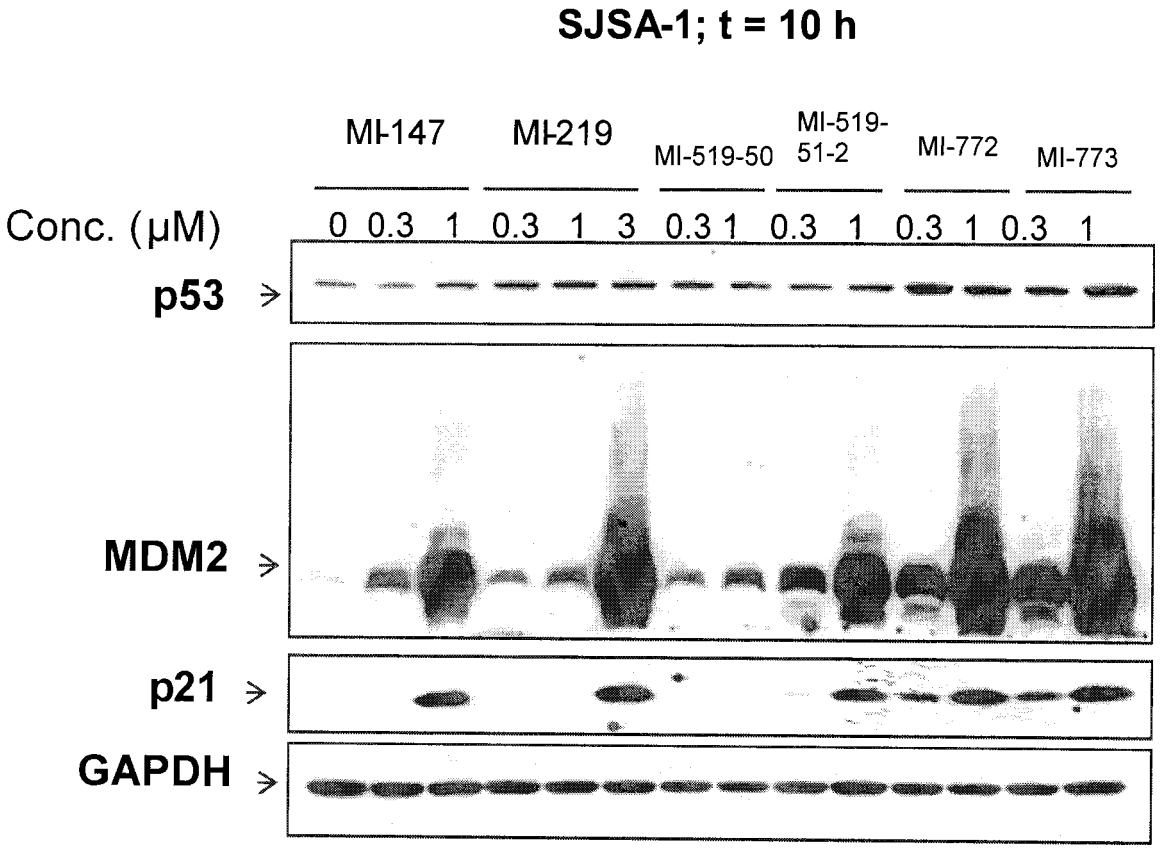

SJSA-1; t = 10 h
MI-147
MI-219
MI-519-50
MI-519-51-2
MI-772
MI-773
Conc. (μM)
0 0.3 1 0.3 1 3 0.3 1 0.3 1 0.3 1 0.3 1
p53
MDM2
p21
GAPDH

FIG. 5

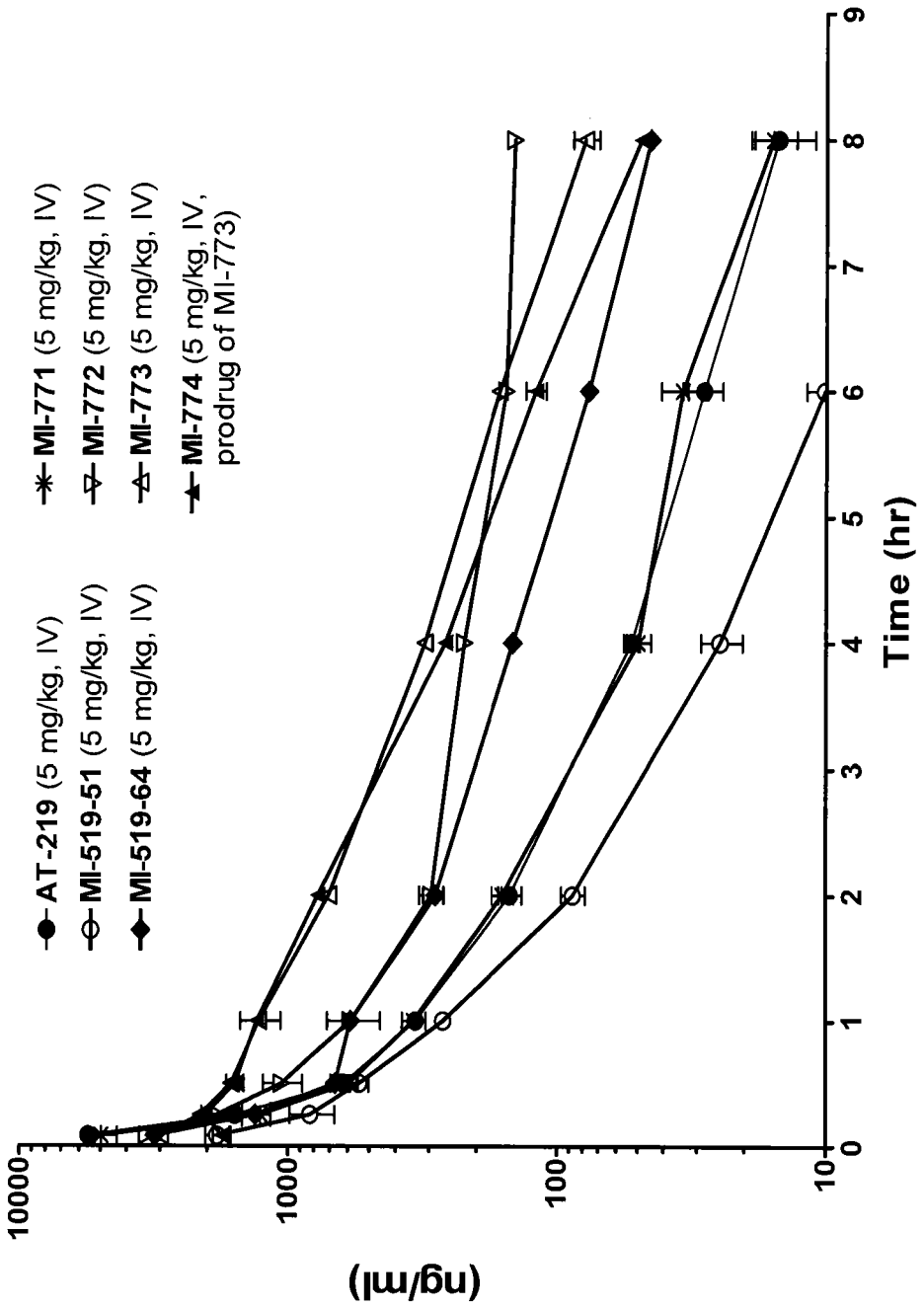

AT-219 (5 mg/kg, IV)
MI-519-51 (5 mg/kg, IV)
MI-519-64 (5 mg/kg, IV)
MI-771 (5 mg/kg, IV)
MI-772 (5 mg/kg, IV)
MI-773 (5 mg/kg, IV)
MI-774 (5 mg/kg, IV, prodrug of MI-773)
(ng/ml)
10000
1000
100
10
0
1
2
3
4
5
6
7
8
9
Time (hr)

FIG. 6

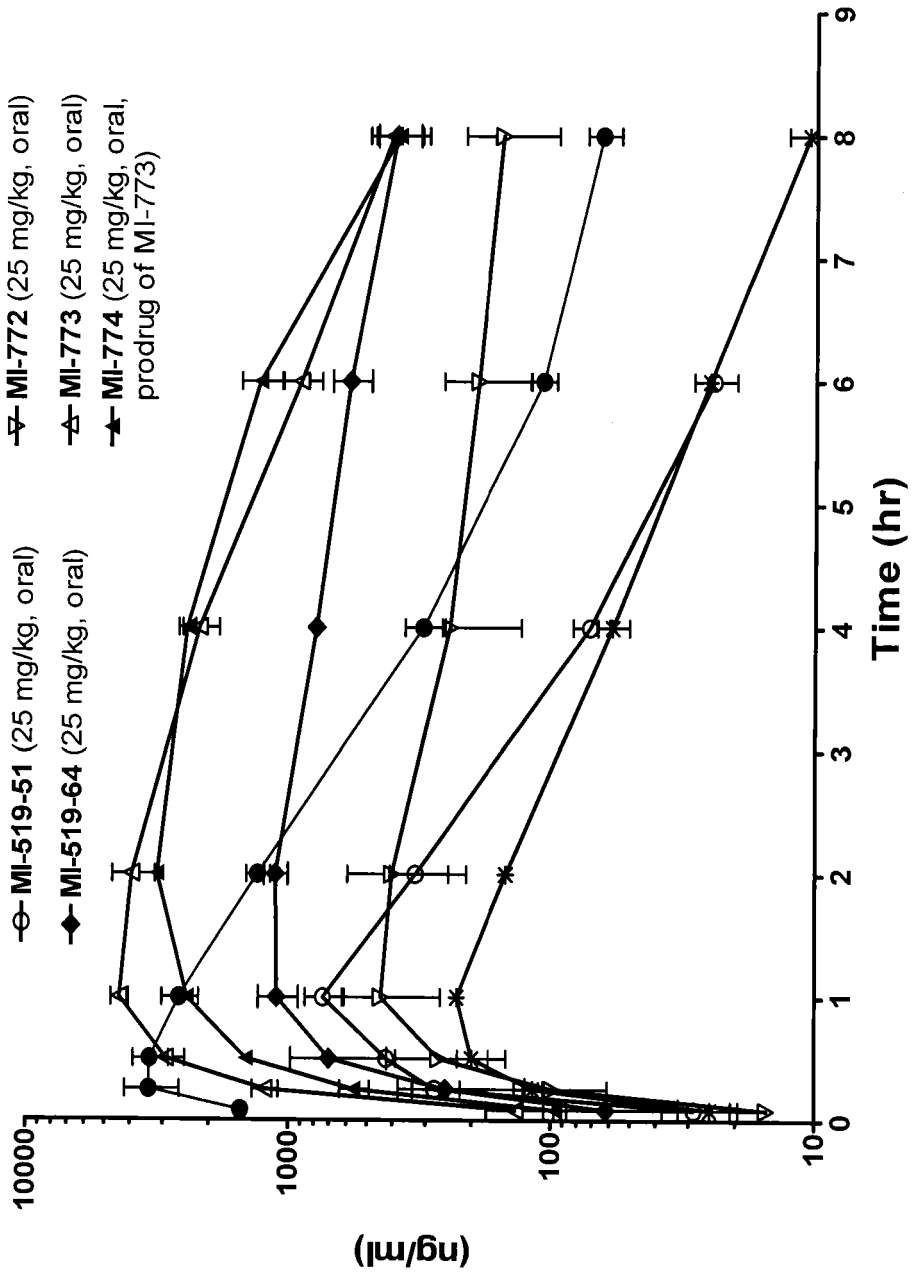
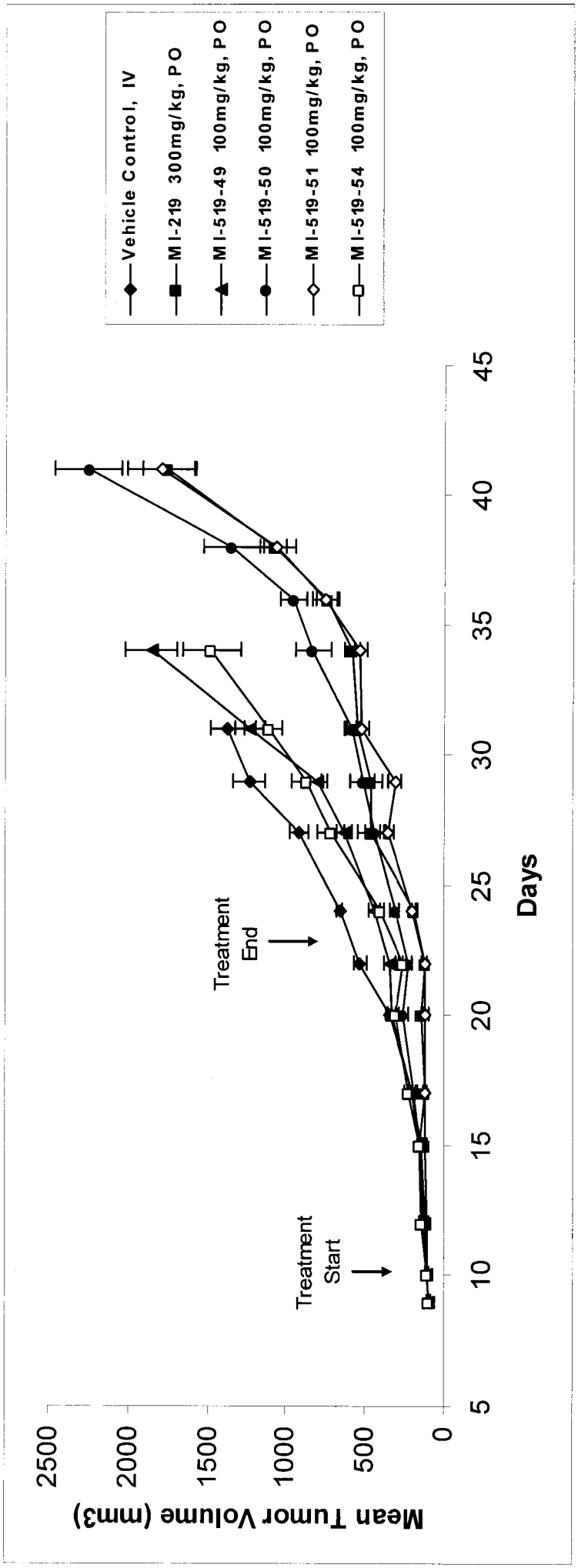

AT-219 (25 mg/kg, oral)
MI-519-51 (25 mg/kg, oral)
MI-519-64 (25 mg/kg, oral)
MI-771 (25 mg/kg, oral)
MI-772 (25 mg/kg, oral)
MI-773 (25 mg/kg, oral)
MI-774 (25 mg/kg, oral, prodrug of MI-773)
10000
1000
100
10
(ng/ml)
0
1
2
3
4
5
6
7
8
9
Time (hr)

FIG. 7


Vehicle Control, IV
MI-219 300mg/kg, PO
MI-519-49 100mg/kg, PO
MI-519-50 100mg/kg, PO
MI-519-51 100mg/kg, PO
MI-519-54 100mg/kg, PO
Mean Tumor Volume (mm3)
2500
2000
1500
1000
500
0
5
10
15
20
25
30
35
40
45
Days
Treatment Start
Treatment End

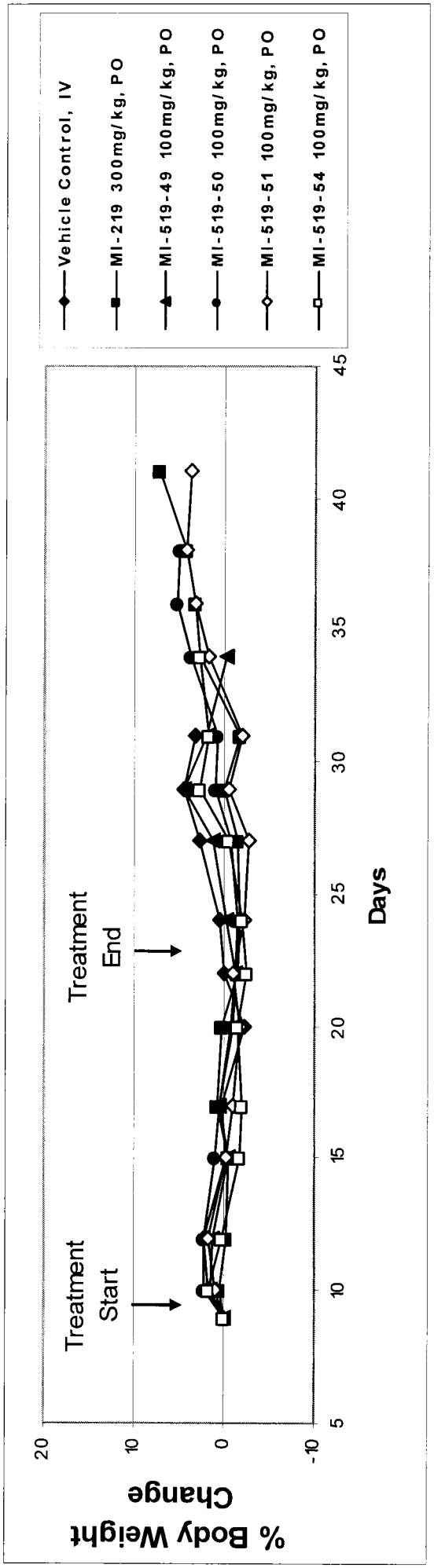
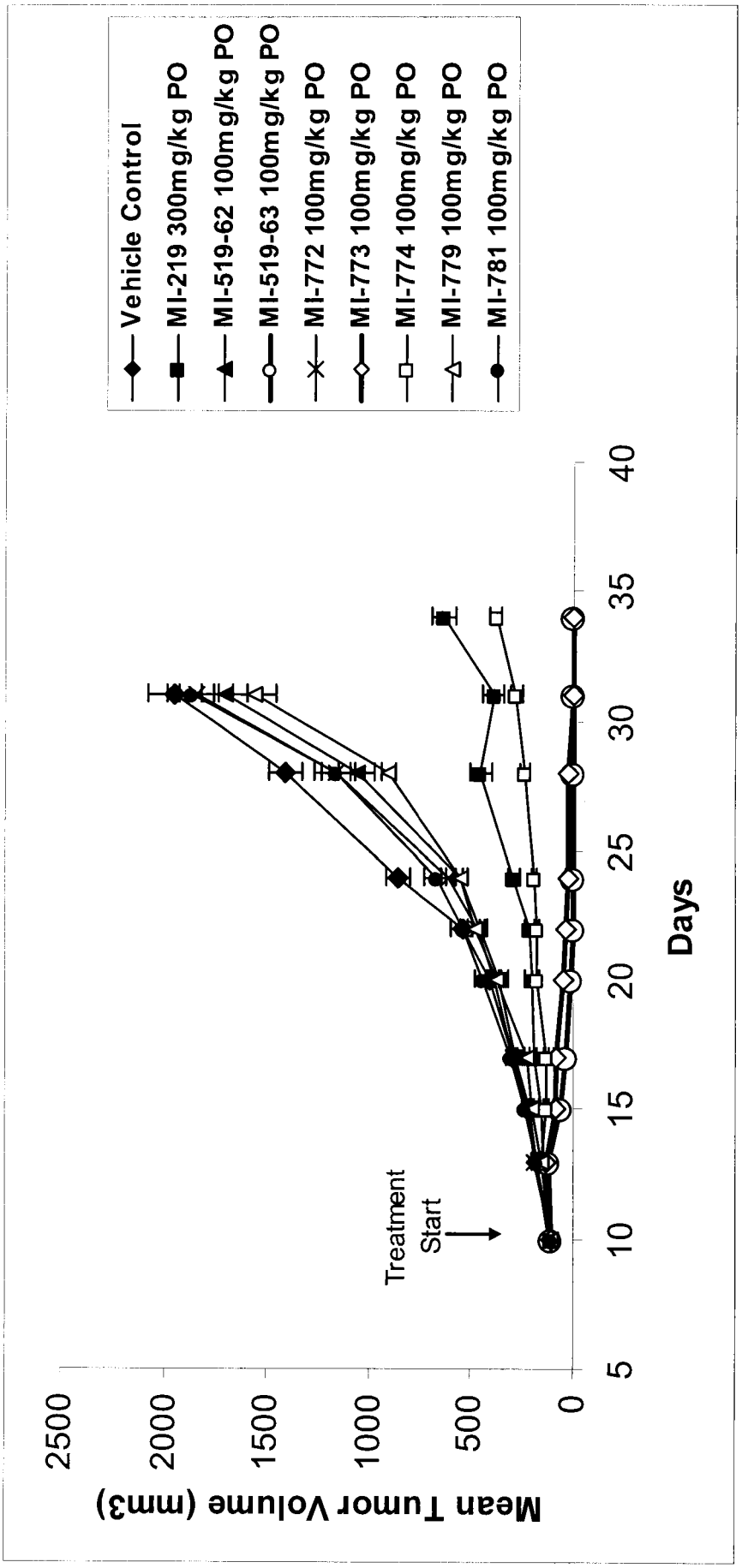

% Body Weight Change
20
10
0
-10
5
10
15
20
25
30
35
40
45
Days
Treatment Start
Treatment End
Vehicle Control, IV
MI-219 300mg/kg, PO
MI-519-49 100mg/kg, PO
MI-519-50 100mg/kg, PO
MI-519-51 100mg/kg, PO
MI-519-54 100mg/kg, PO

FIG. 8

FIG. 9


Vehicle Control
MI-219 300mg/kg PO
MI-519-62 100mg/kg PO
MI-519-63 100mg/kg PO
MI-772 100mg/kg PO
MI-773 100mg/kg PO
MI-774 100mg/kg PO
MI-779 100mg/kg PO
MI-781 100mg/kg PO
Mean Tumor Volume (mm3)
2500
2000
1500
1000
500
0
Treatment Start
5
10
15
20
25
30
35
40
Days

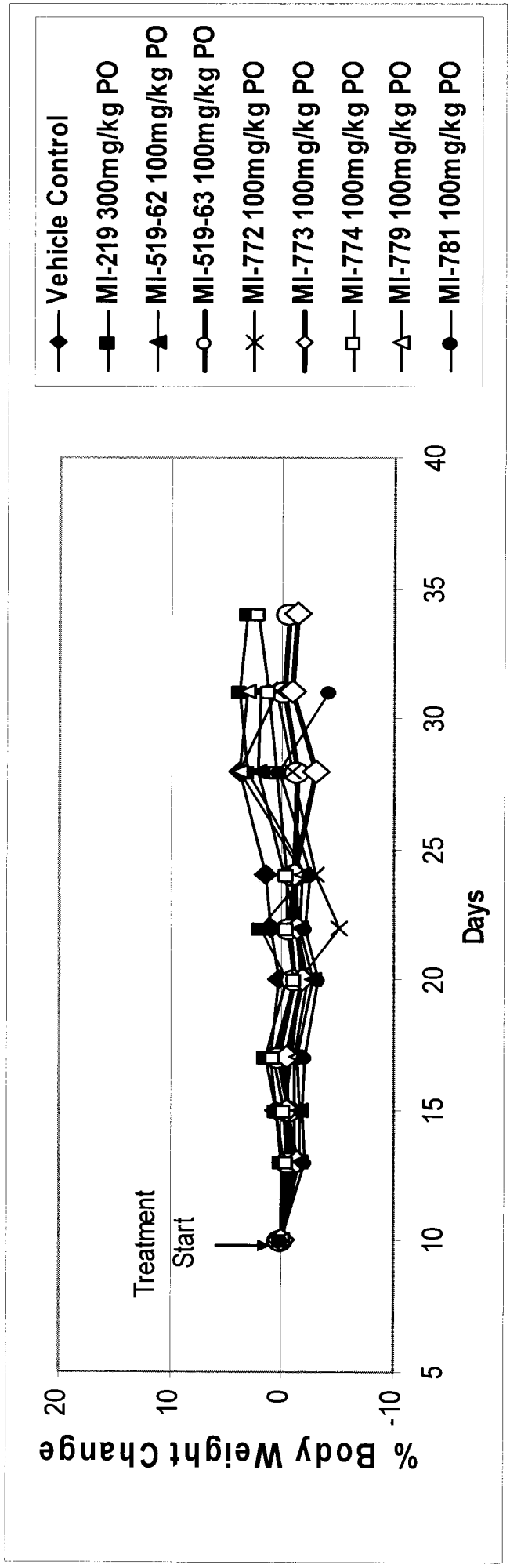

Vehicle Control
MI-219 300mg/kg PO
MI-519-62 100mg/kg PO
MI-519-63 100mg/kg PO
MI-772 100mg/kg PO
MI-773 100mg/kg PO
MI-774 100mg/kg PO
MI-779 100mg/kg PO
MI-781 100mg/kg PO
% Body Weight Change
20
10
0
-10
5
10
15
20
25
30
35
40
Days
Treatment
Start

FIG. 10

FIG. 11

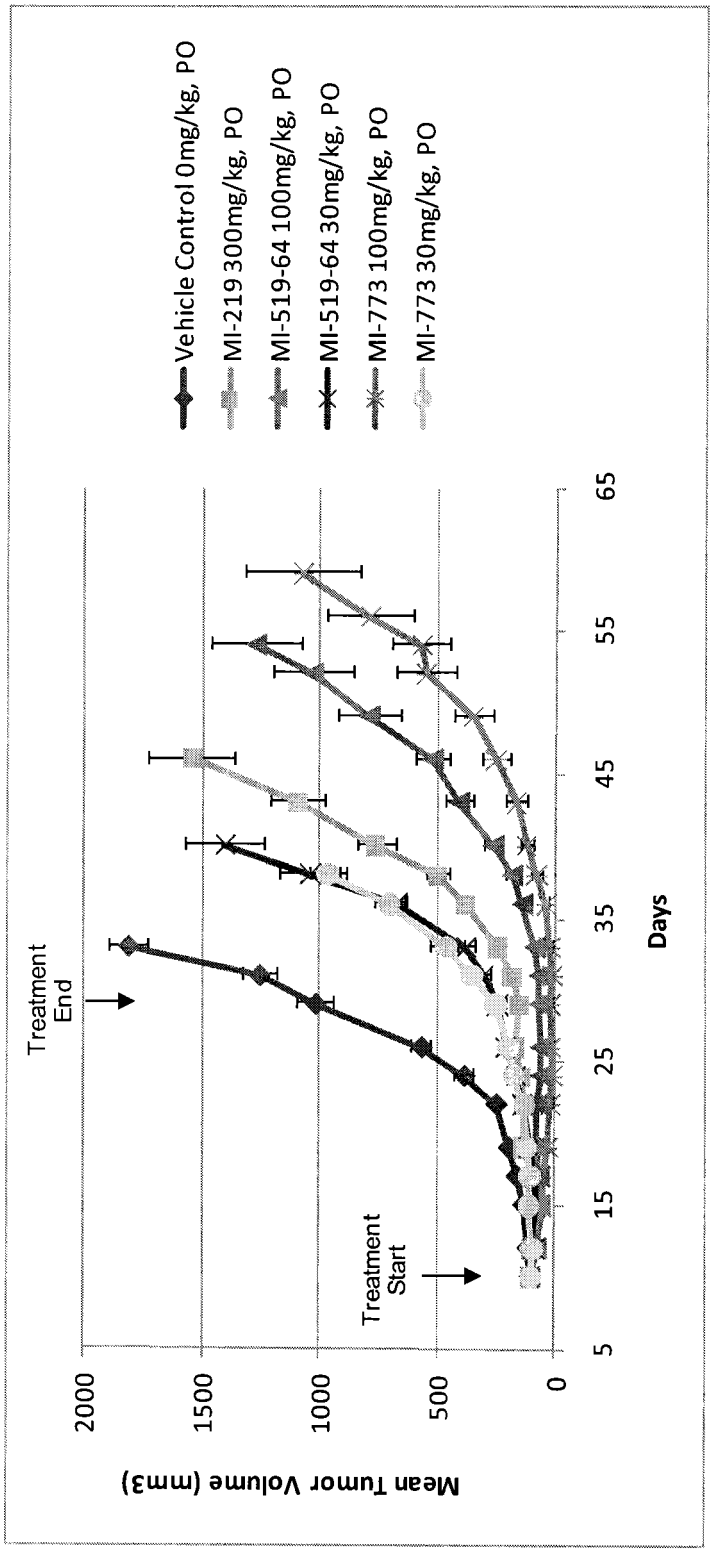

Vehicle Control 0mg/kg, PO
MI-219 300mg/kg, PO
MI-519-64 100mg/kg, PO
MI-519-64 30mg/kg, PO
MI-773 100mg/kg, PO
MI-773 30mg/kg, PO
Mean Tumor Volume (mm3)
2000
1500
1000
500
0
Treatment End
Treatment Start
5
15
25
35
45
55
65
Days

FIG. 12

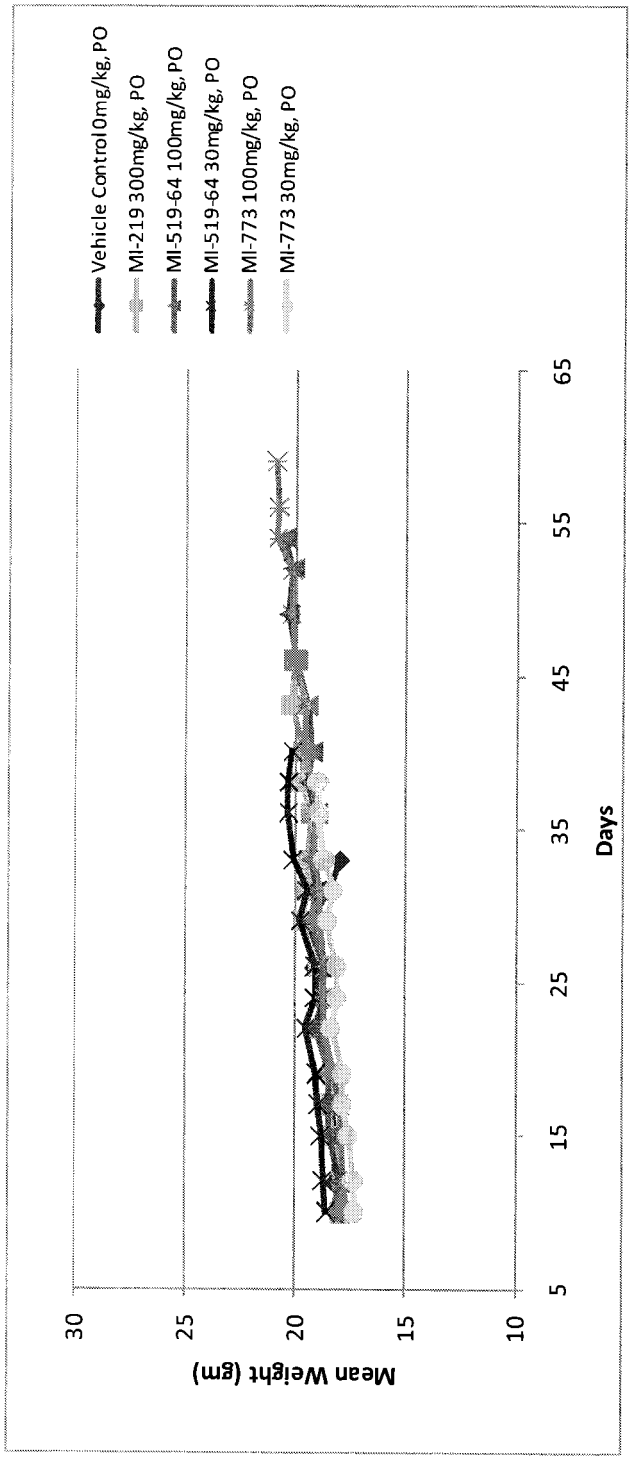

Vehicle Control 0mg/kg, PO
MI-219 300mg/kg, PO
MI-519-64 100mg/kg, PO
MI-519-64 30mg/kg, PO
MI-773 100mg/kg, PO
MI-773 30mg/kg, PO
Mean Weight (gm)
30
25
20
15
10
5
15
25
35
45
55
65
Days

FIG. 13A

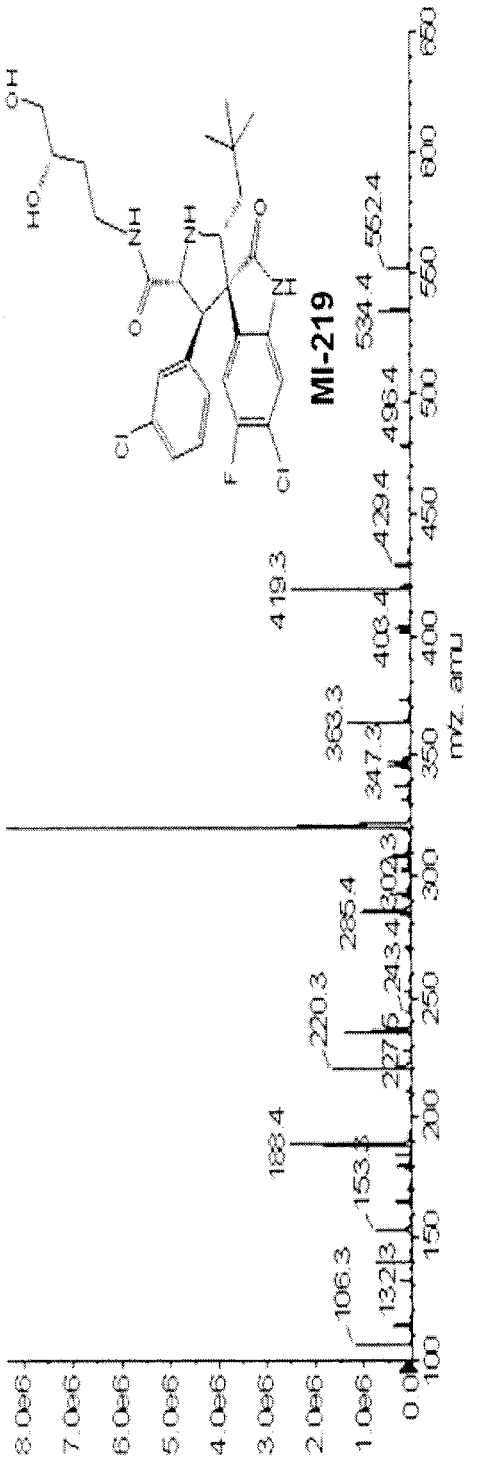

MI-219
m/z, amu
320.3
106.3
132.3
153.3
188.4
220.3
227.5
243.4
285.4
302.3
347.3
363.3
419.3
429.4
498.4
534.4
552.4

FIG. 13B

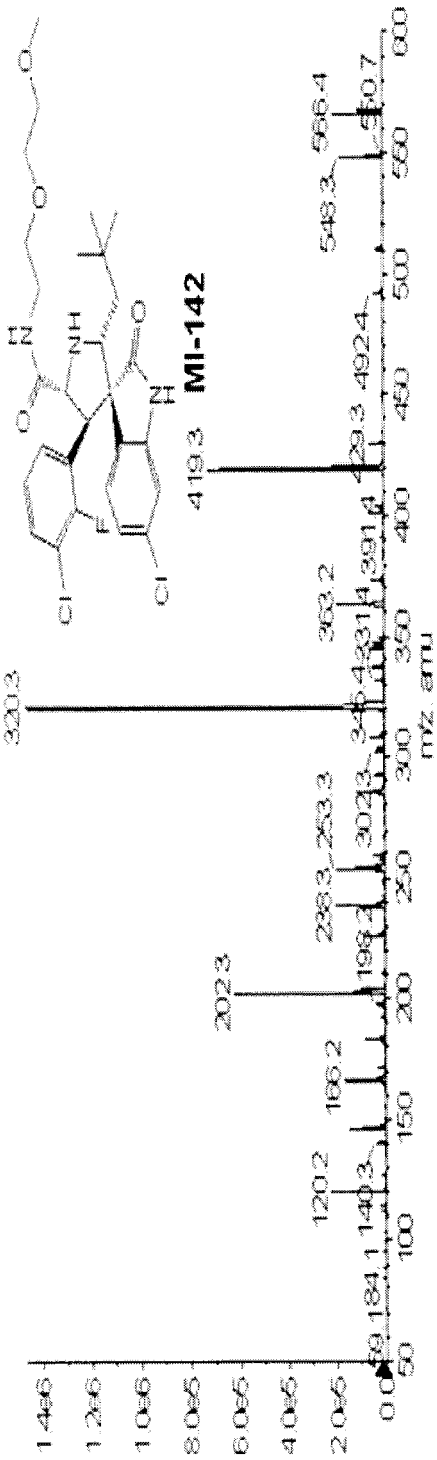


FIG. 13C

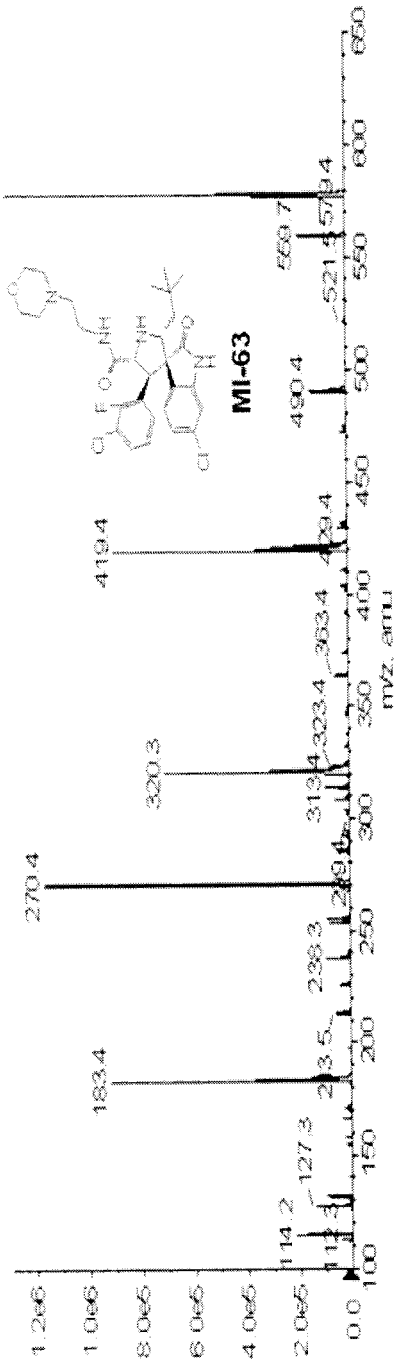

MI-63
m/z, amu
577.5
579.4
580.7
521.4
490.4
419.4
421.4
363.4
323.4
320.3
313.4
270.4
238.3
235
183.4
127.3
114.2
100
150
200
250
300
350
400
450
500
550
600
650
0.0
2.0e6
4.0e6
6.0e6
8.0e6
1.0e6
1.2e6

FIG. 13D

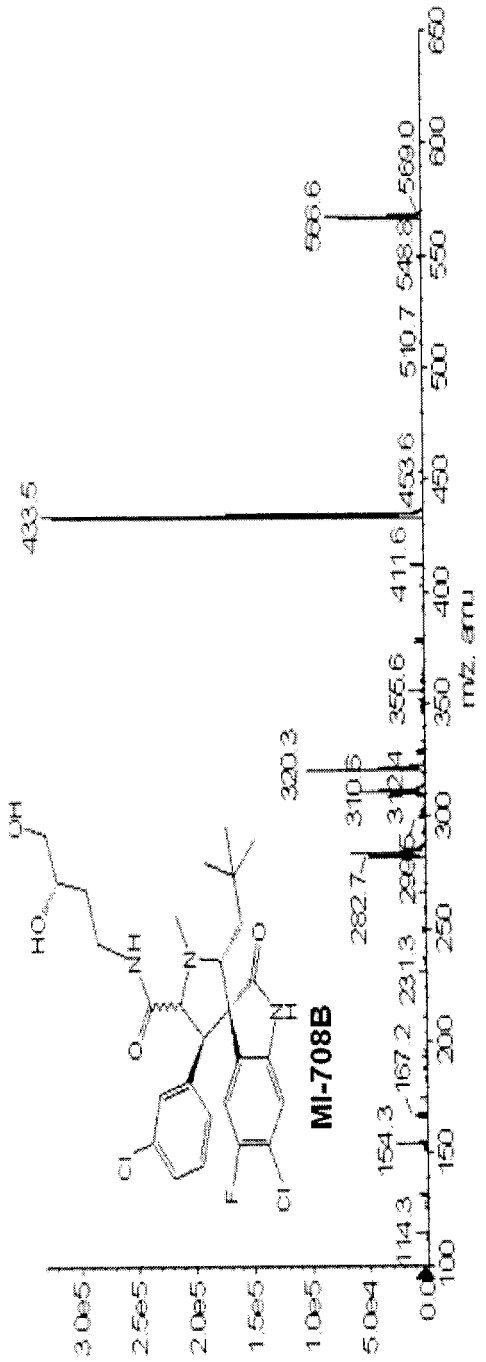

MI-708B
m/z, amu
433.5
320.3
282.7
154.3
114.3
167.2
231.3
355.6
411.6
453.6
510.7
548.8
569.0
596.6

FIG. 14A

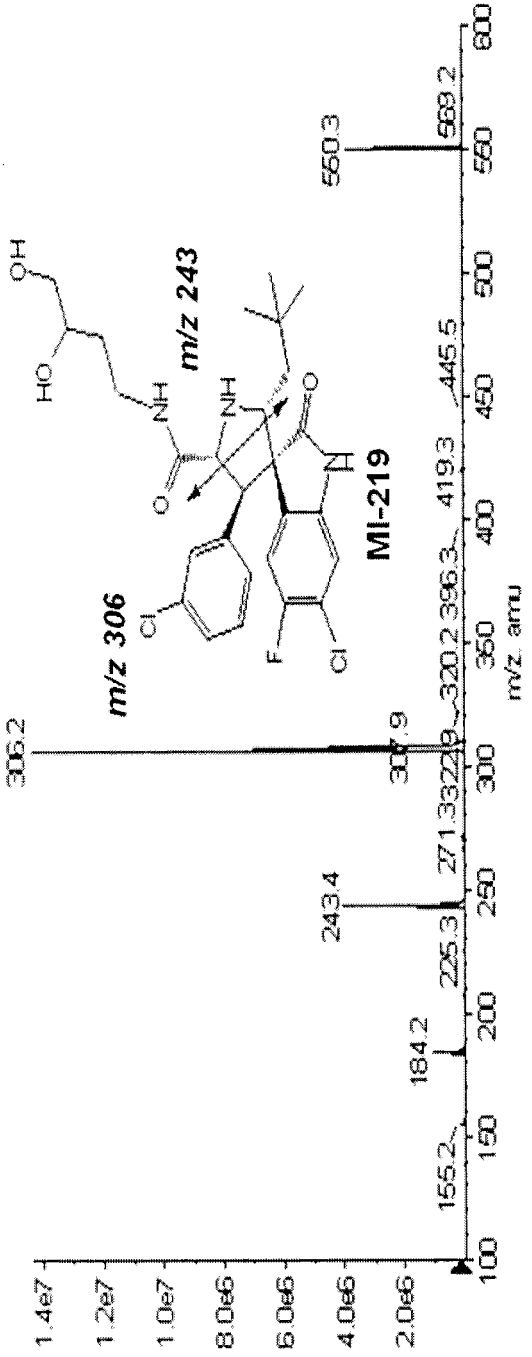


FIG. 14B

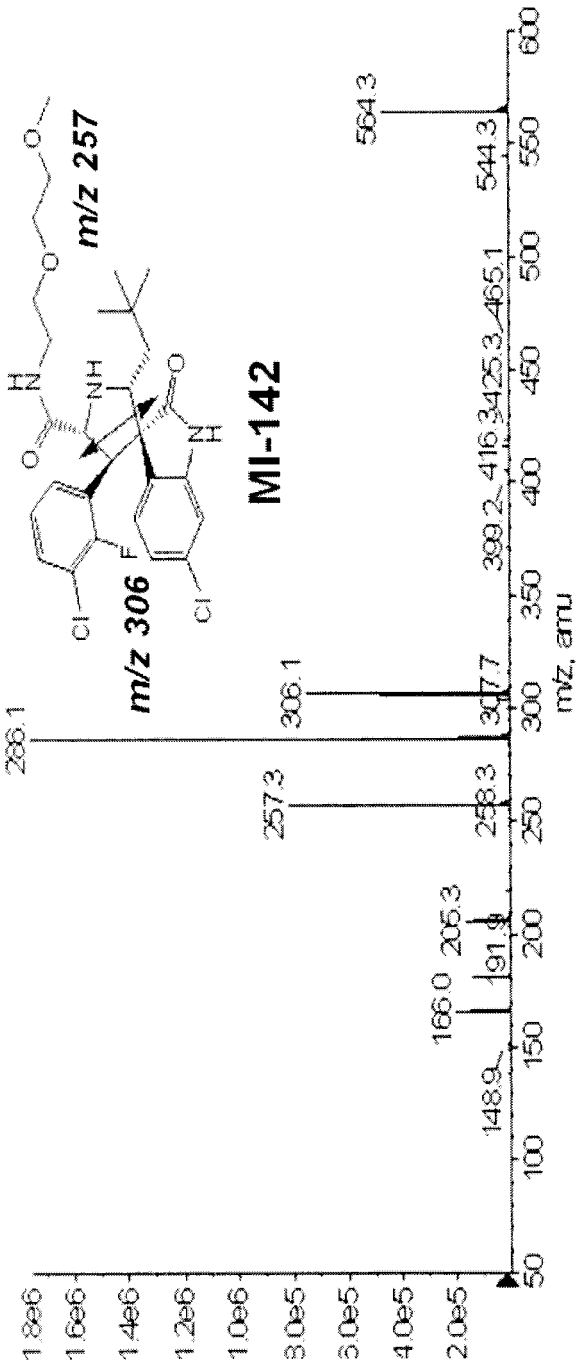

MI-142
m/z 306
m/z 257
m/z, amu
286.1
306.1
257.3
258.3
307.7
205.3
191.9
166.0
148.9
564.3
544.3
465.1
425.3
416.3
399.2
1.8e6
1.6e6
1.4e6
1.2e6
1.0e6
3.0e5
3.0e5
4.0e5
2.0e5
50
100
150
200
250
300
350
400
450
500
550
600

FIG. 15A

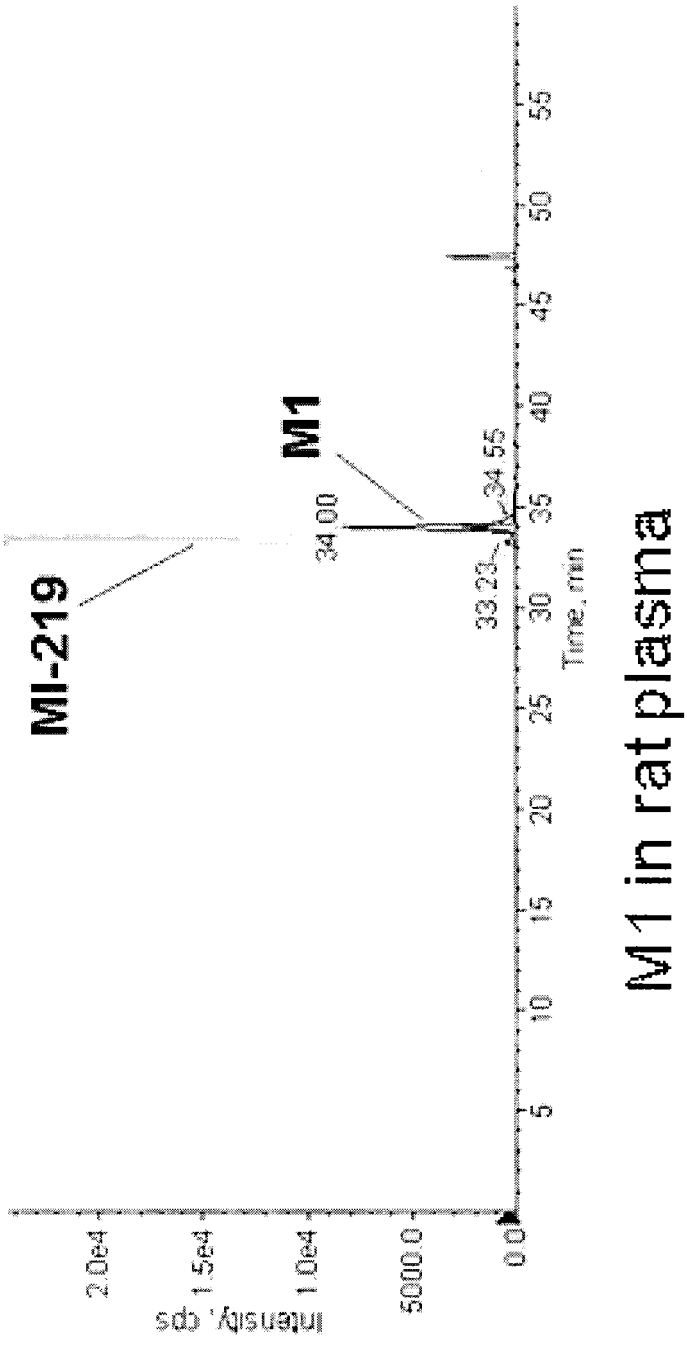

MI-219
M1
34.00
34.55
33.23
Time, min
Intensity, cps
2.0e4
1.5e4
1.0e4
5000.0
0.0
0
5
10
15
20
25
30
35
40
45
50
55
M1 in rat plasma

FIG. 15B

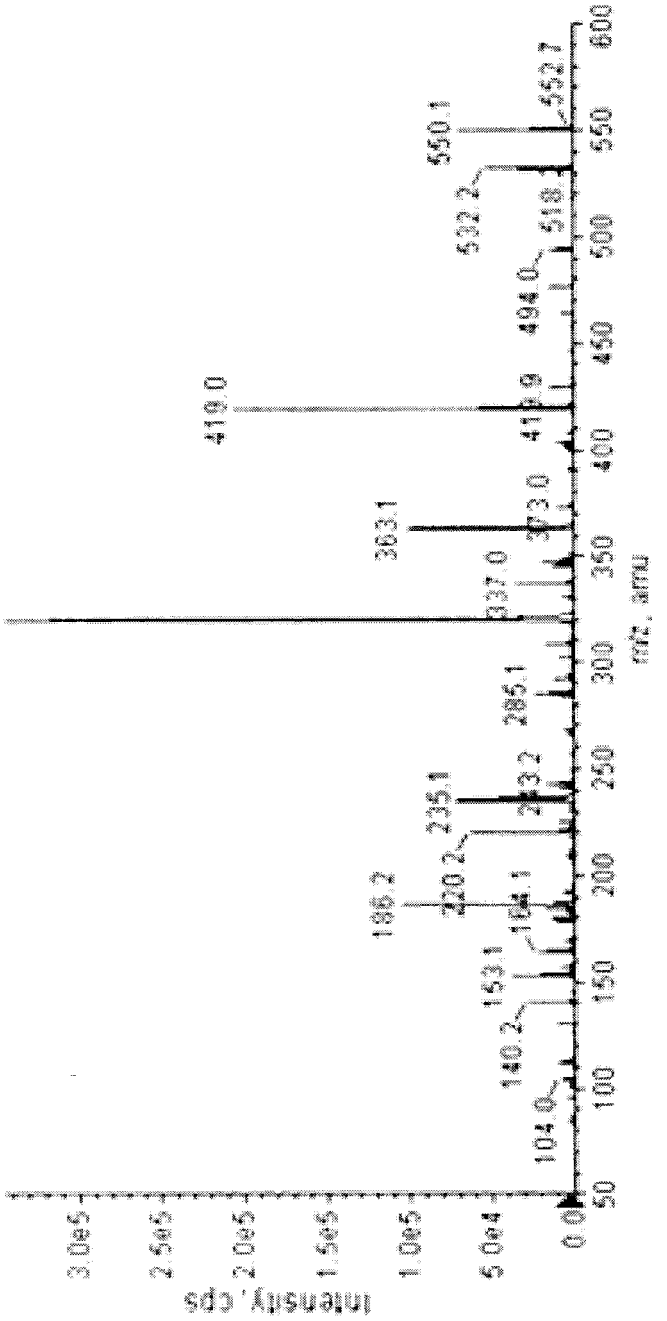
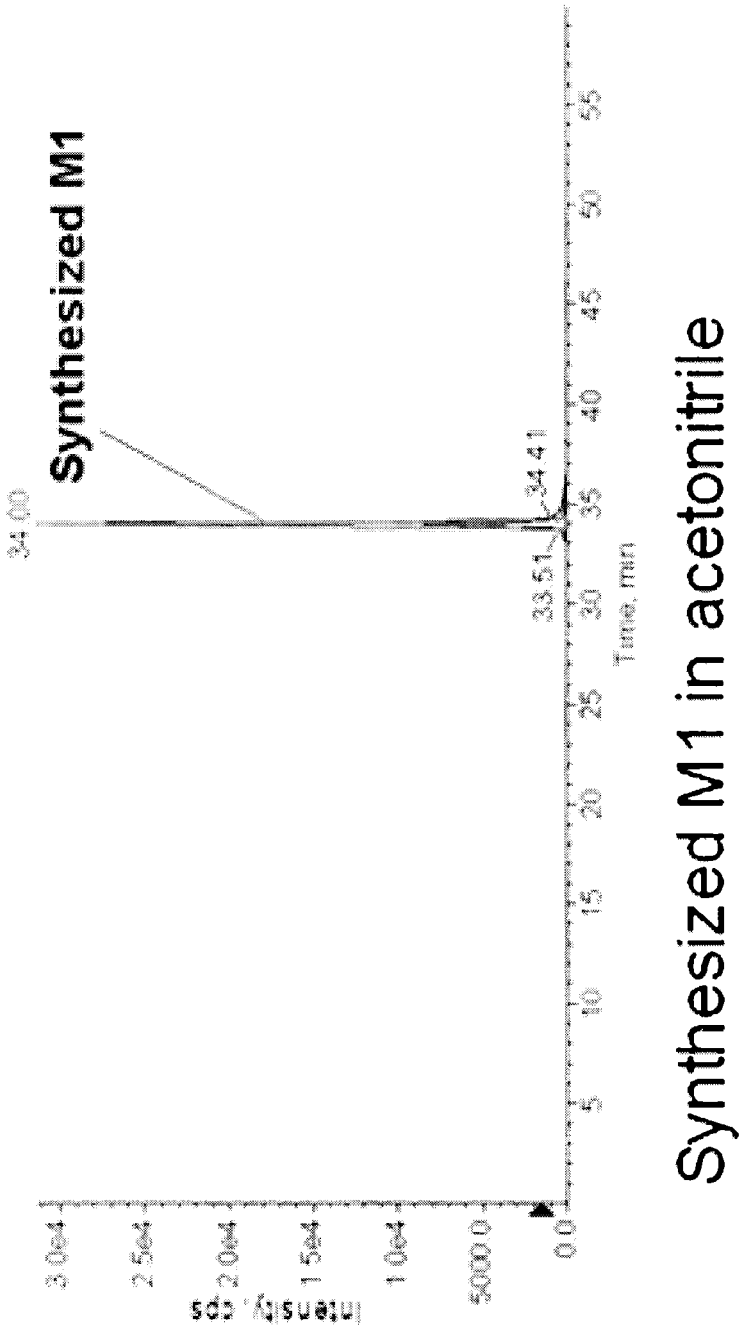

MS/MS spectrum of M1 in rat plasma
Intensity, cps
m/z, amu
320.0
419.0
363.1
337.0
285.1
235.1
220.2
186.2
153.1
140.2
104.0
494.0
532.2
550.1
552.7

FIG. 15C



Synthesized M1 in acetonitrile

FIG. 15D

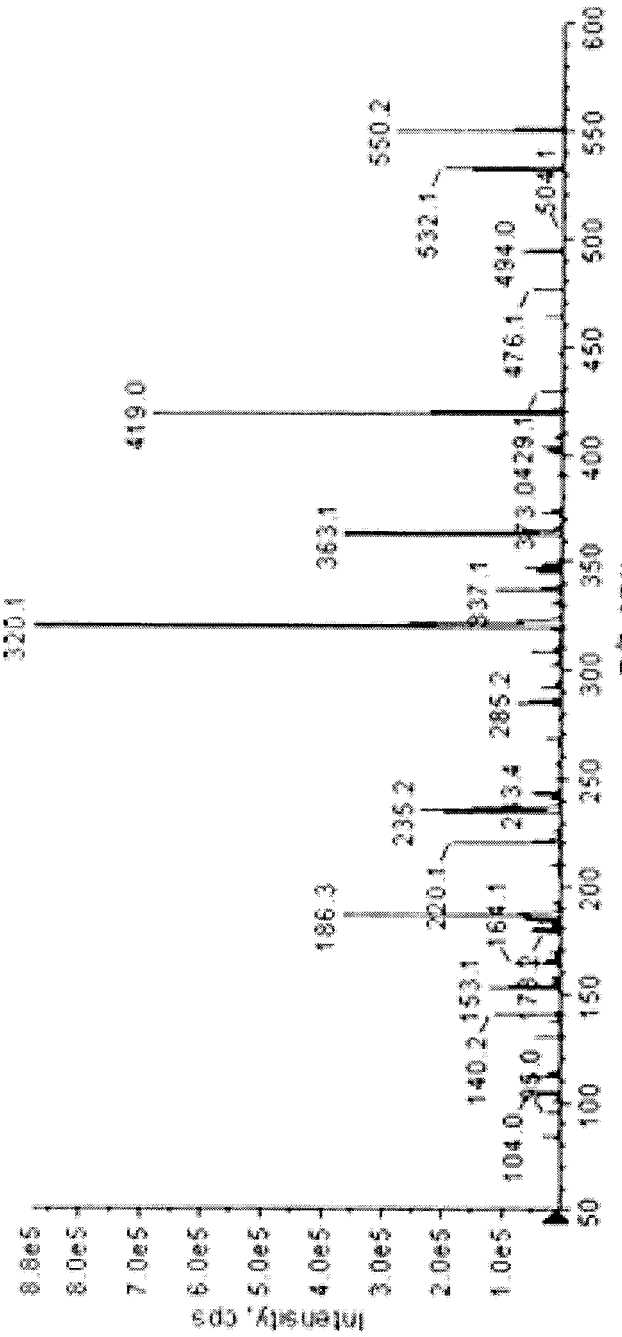

MS/MS spectrum of synthesized M1
Intensity, cps
m/z, amu
320.1
419.0
363.1
537.1
550.2
532.1
476.1
484.0
429.1
285.2
235.2
220.1
186.3
153.1
140.2
104.0

FIG. 16

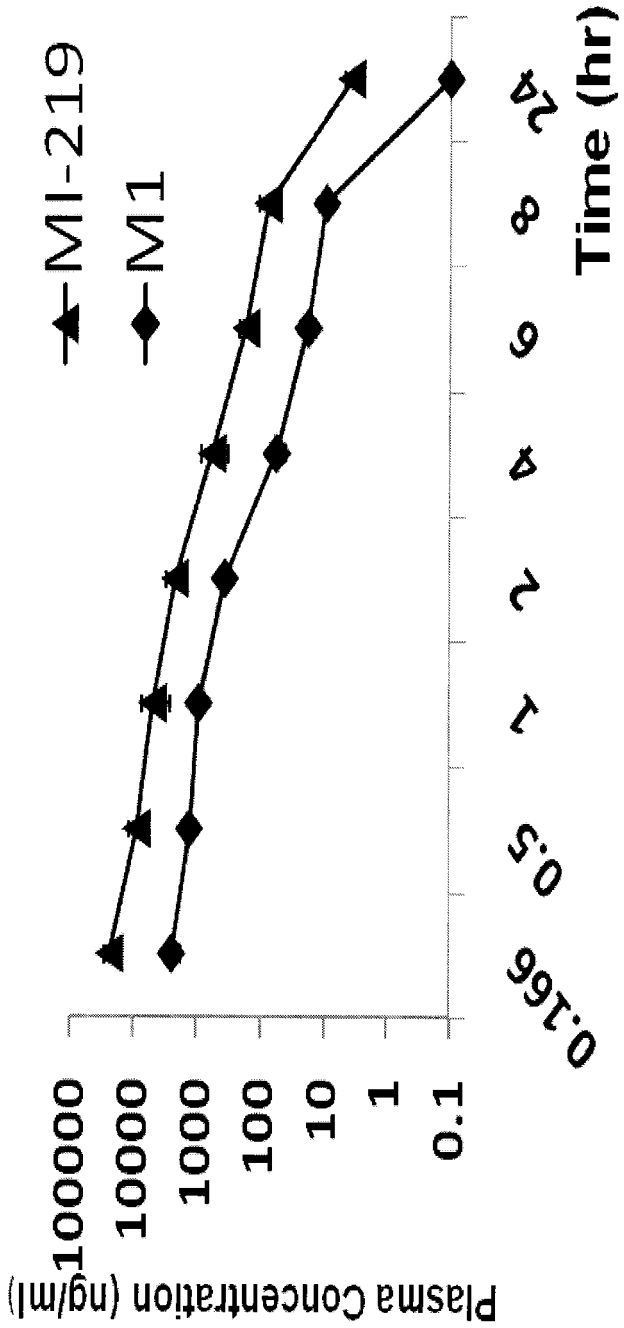

MI-219
M1
Time (hr)
0.166
0.5
1
2
4
8
24
Plasma Concentration (ng/ml)
100000
10000
1000
100
10
1
0.1

FIG. 17A

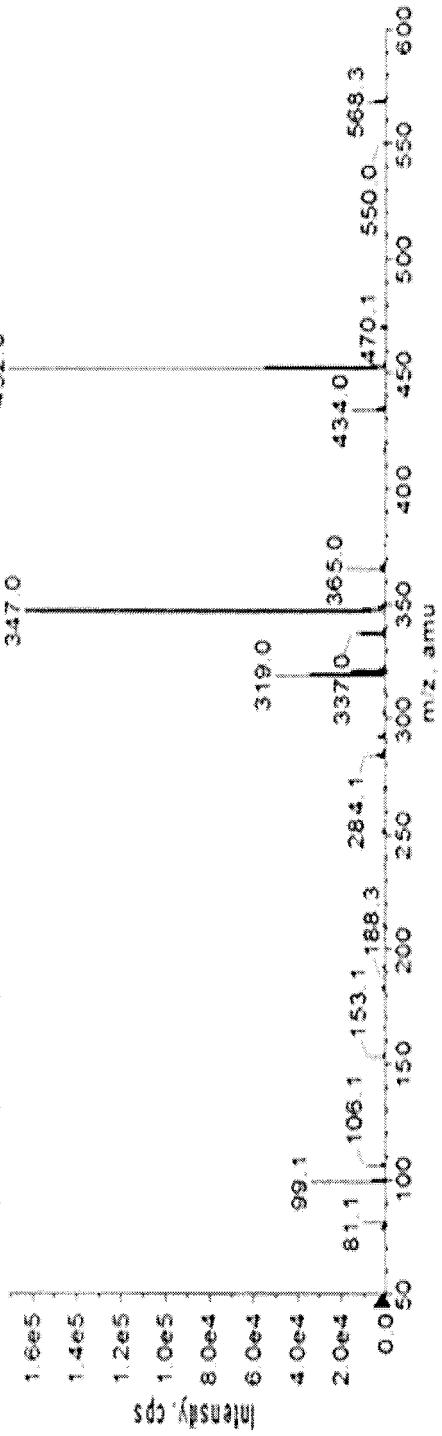

+EPI (568.30) CE (45) 5.071 to 5.270 min
Intensity, cps
m/z, amu
452.0
347.0
319.0
337.0
365.0
434.0
470.1
550.0
568.3
284.1
188.3
153.1
106.1
99.1
81.1

FIG. 17B

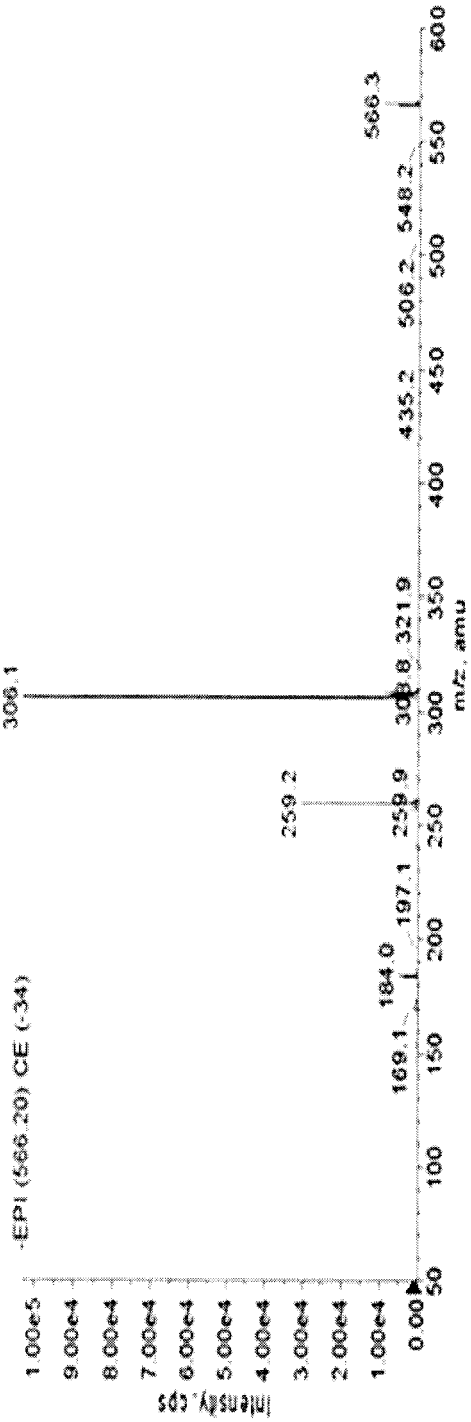

EPI (566.20) CE (-34)
Intensity, cps
m/z, amu
306.1
259.2
566.3
548.2
506.2
435.2
321.9
259.9
197.1
184.0
169.1

FIG. 18A

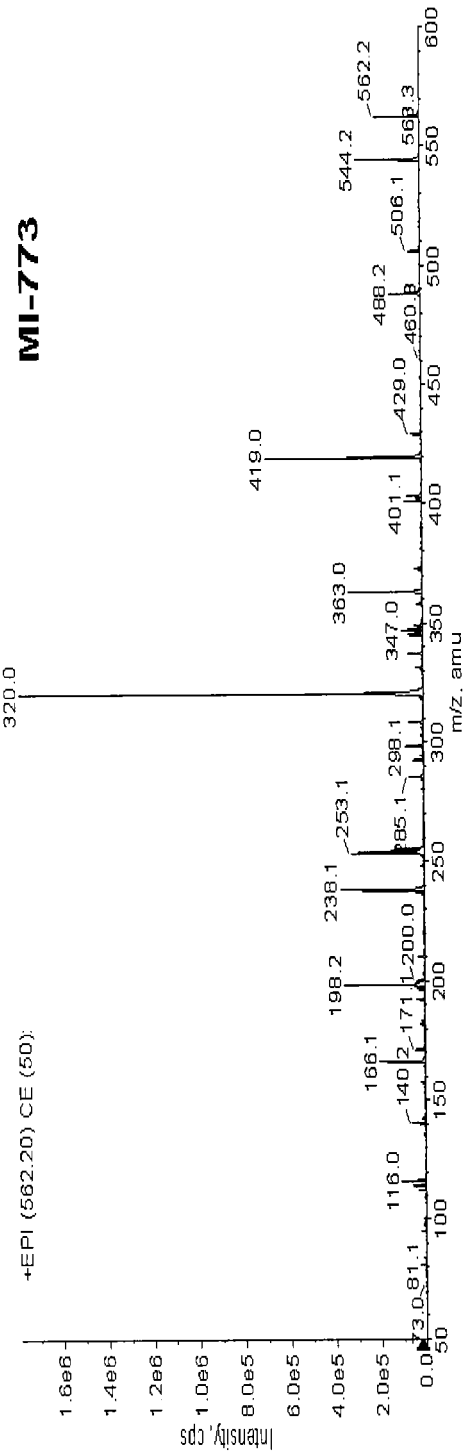

MI-773
+EPI (562.20) CE (50):
Intensity, cps
m/z, amu
320.0
419.0
363.0
347.0
401.1
429.0
460.8
488.2
506.1
544.2
562.2
568.3
253.1
238.1
198.2
166.1
116.0
81.1
73.0

FIG. 18B

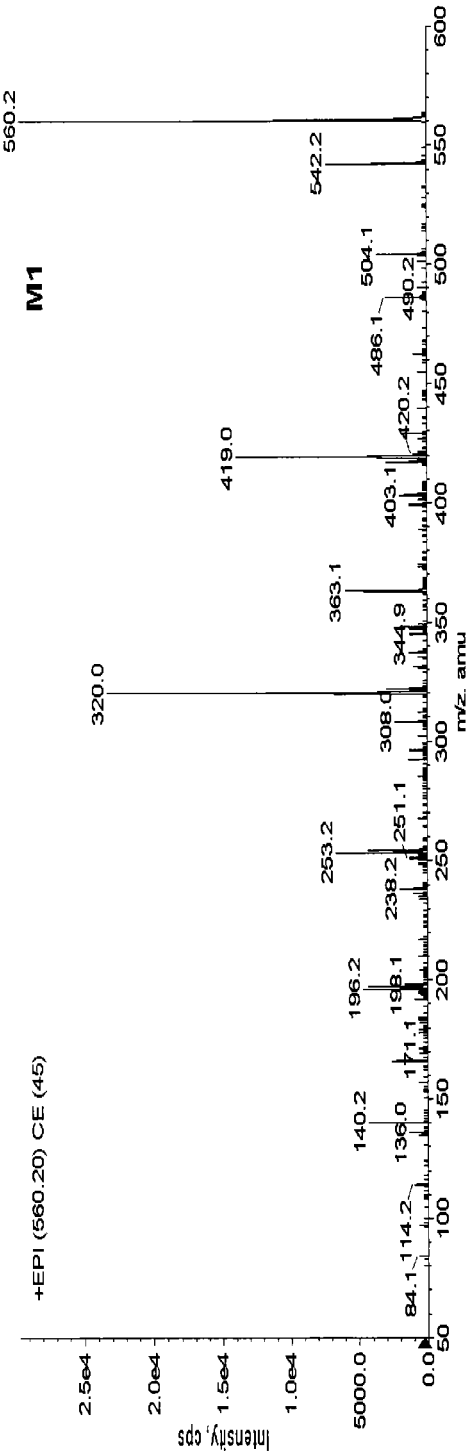

M1
+EPI (560.20) CE (45)
Intensity, cps
m/z, amu
560.2
542.2
504.1
490.2
486.1
420.2
419.0
403.1
363.1
344.9
320.0
308.0
253.2
251.1
238.2
196.2
198.1
140.2
136.0
114.2
84.1

FIG. 18C

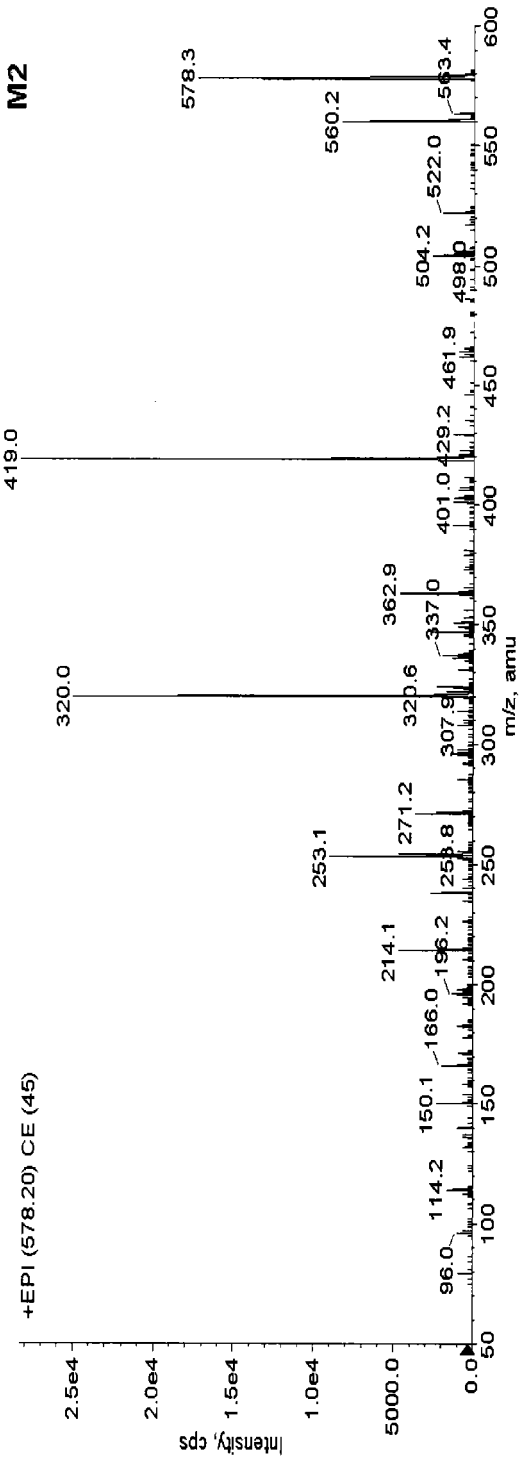

M2
+EPI (578.20) CE (45)
Intensity, cps
m/z, amu
578.3
560.2
563.4
522.0
504.2
498.0
461.9
429.2
419.0
401.0
362.9
337.0
320.0
320.6
307.9
271.2
253.1
214.1
196.2
166.0
150.1
114.2
96.0

FIG. 18D

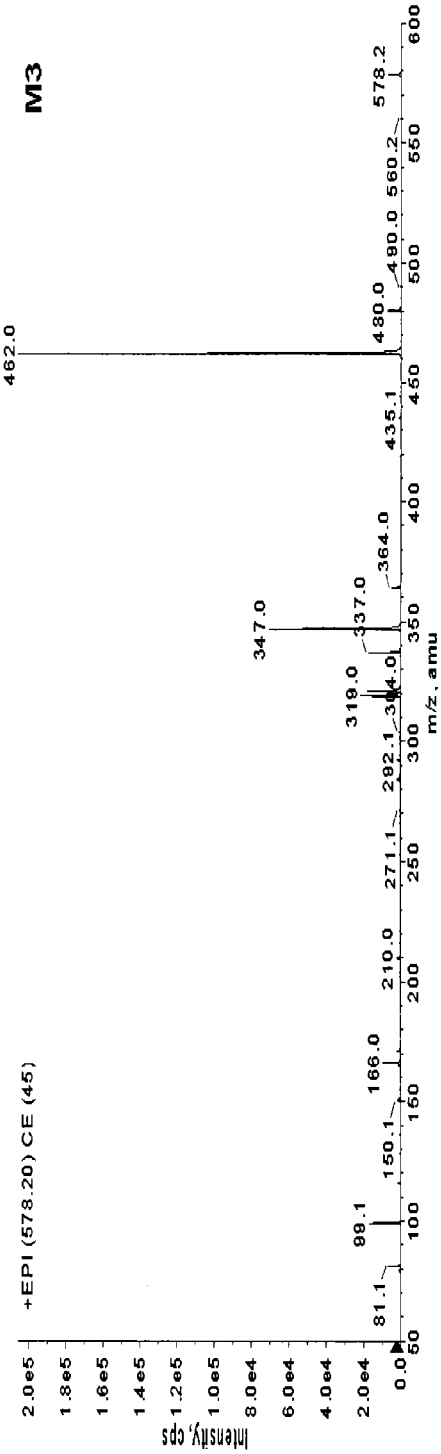

M3
+EPI (578.20) CE (45)
Intensity, cps
m/z, amu
462.0
347.0
578.2
560.2
490.0
480.0
435.1
364.0
337.0
319.0
292.1
271.1
210.0
166.0
150.1
99.1
81.1

FIG. 19A

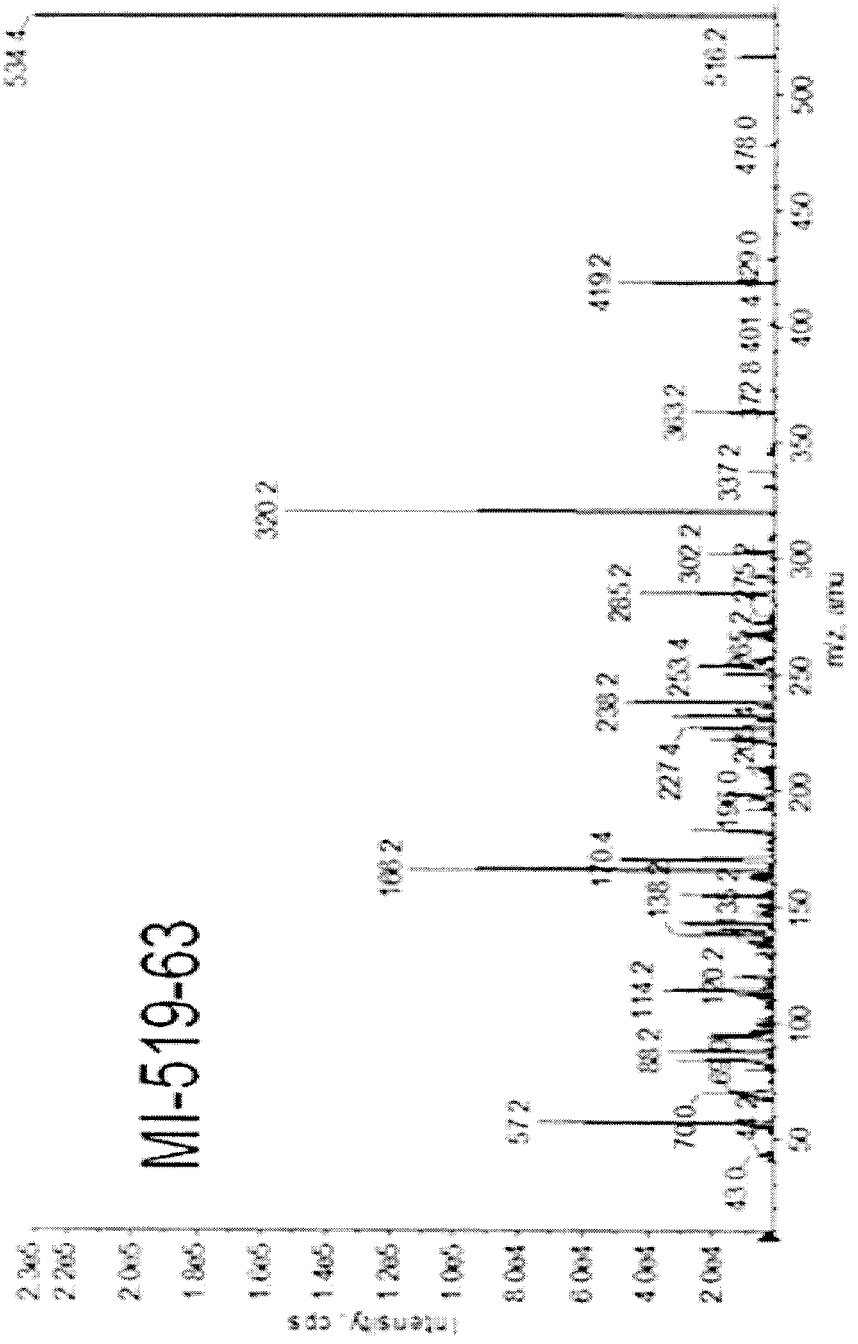


FIG. 19B

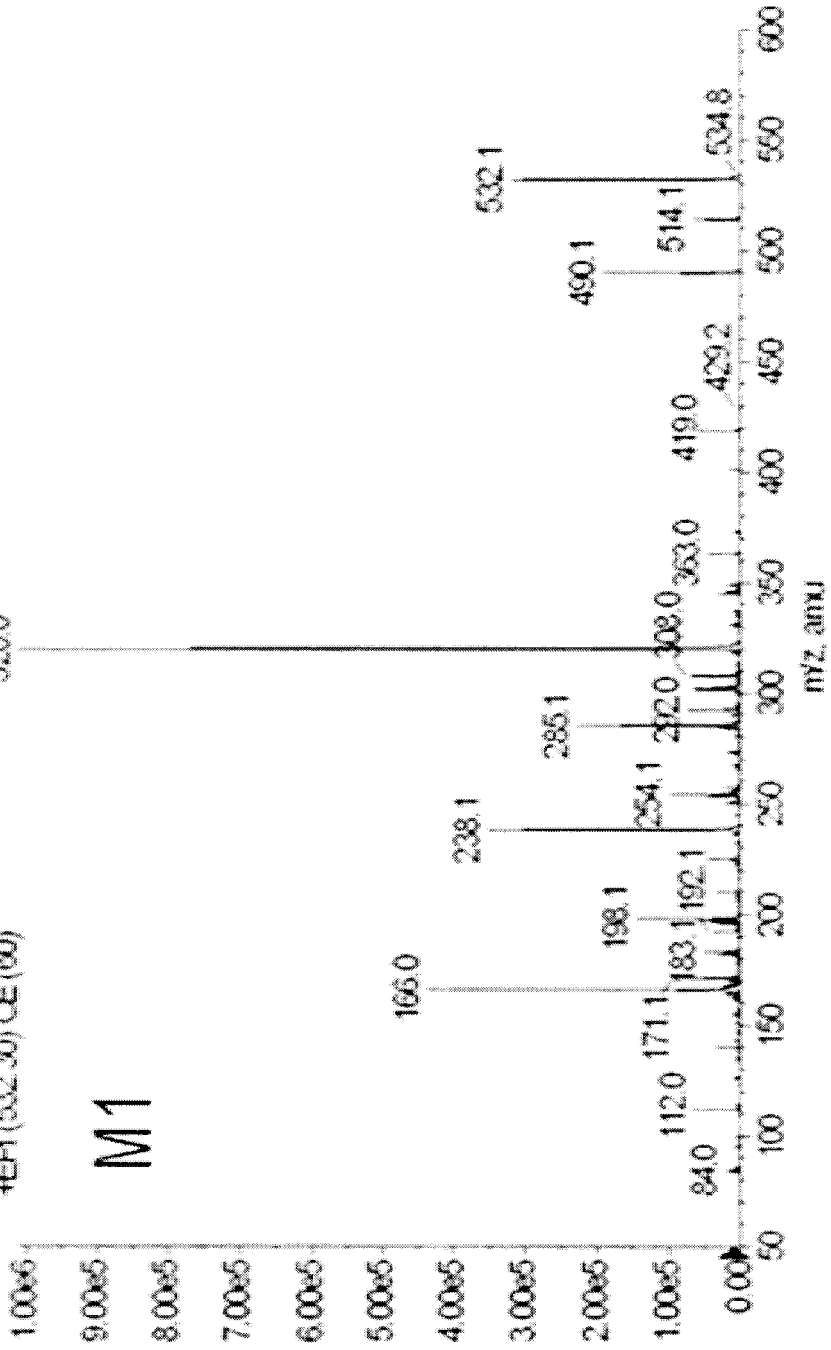
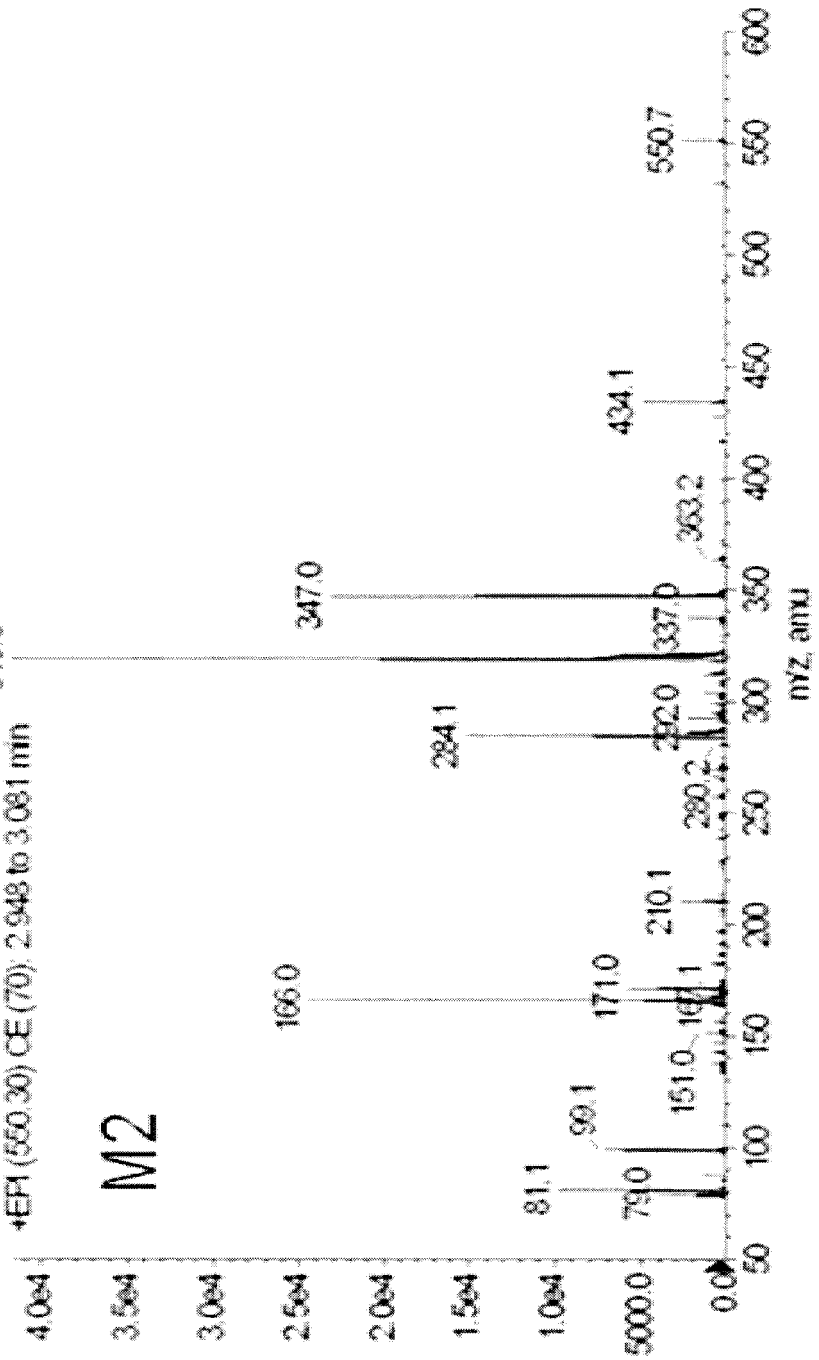

+EPI (532.30) CE (60)
M1
m/z, amu
320.0
308.0
363.0
419.0
429.2
490.1
514.1
532.1
534.8
285.1
292.0
254.1
238.1
198.1
192.1
183.1
171.1
166.0
112.0
84.0

FIG. 19C


+EPI (550.30) CE (70): 2.948 to 3.081 min
M2
m/z, amu
319.0
347.0
166.0
171.0
284.1
210.1
434.1
550.7
363.2
337.0
322.0
280.2
151.0
99.1
81.1
79.0
5000.0
4.0e4
3.5e4
3.0e4
2.5e4
2.0e4
1.5e4
1.0e4
0.0
50
100
150
200
250
300
350
400
450
500
550
600