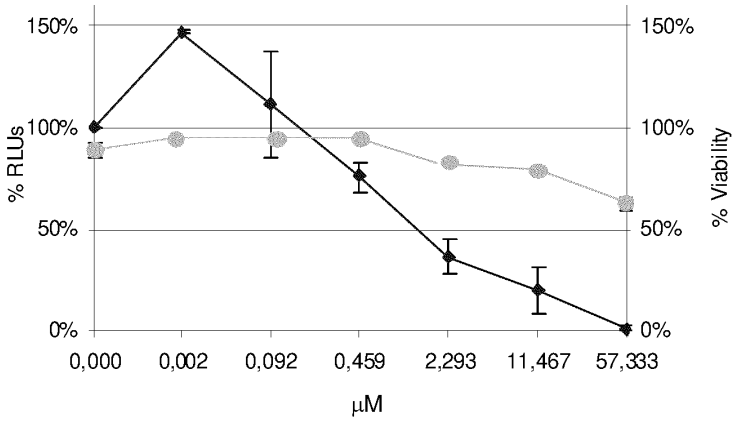


Figure 1A

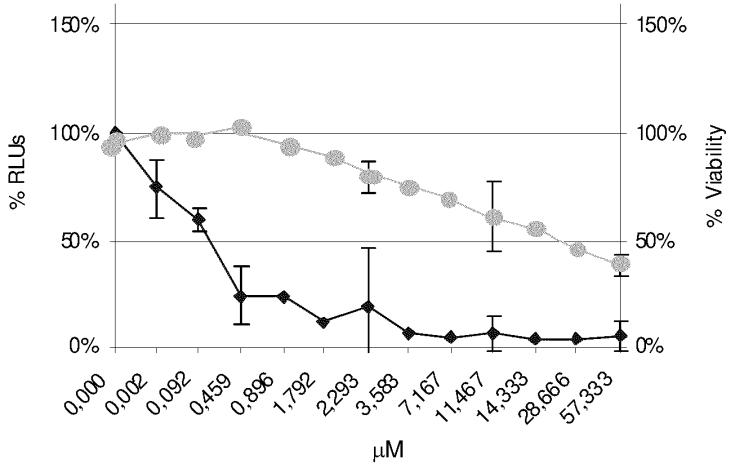


Figure 1B

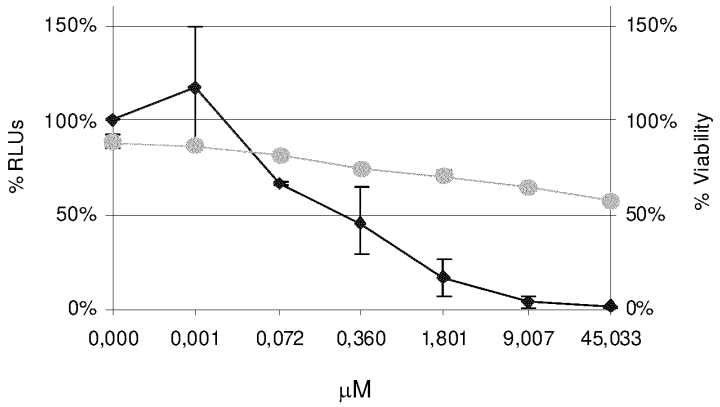


Figure 2A

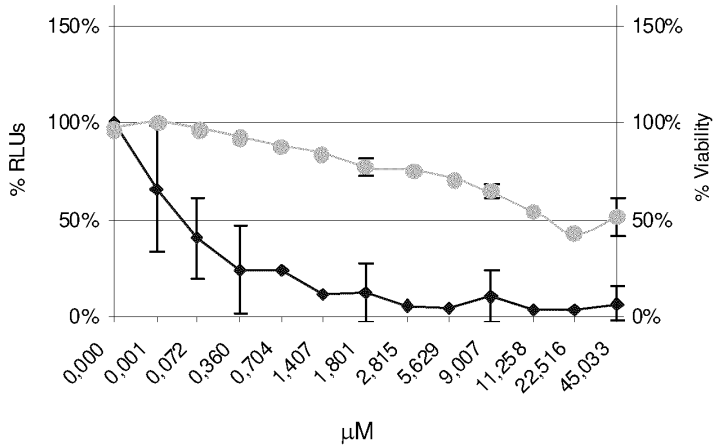


Figure 2B

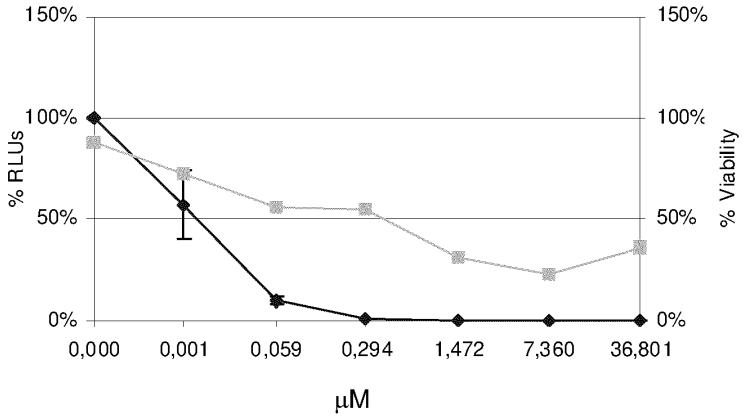


Figure 3A

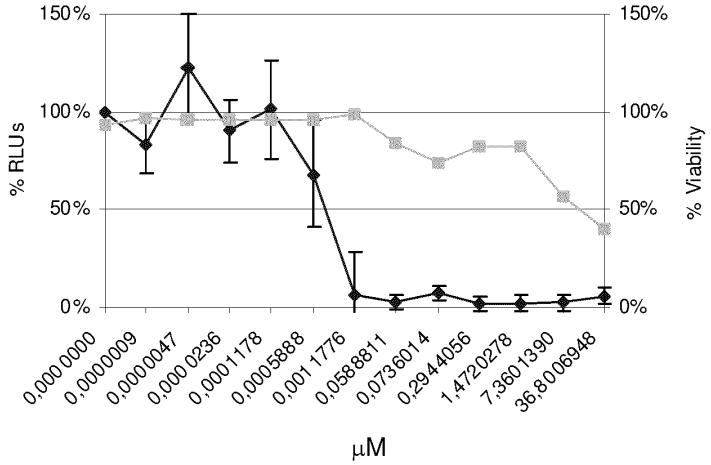


Figure 3B

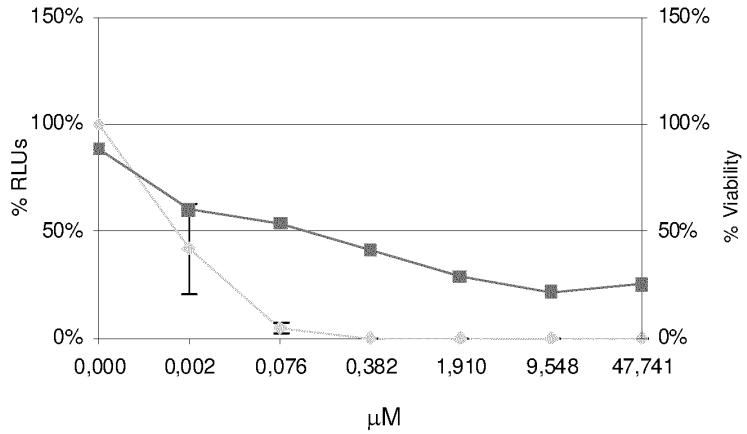


Figure 4A

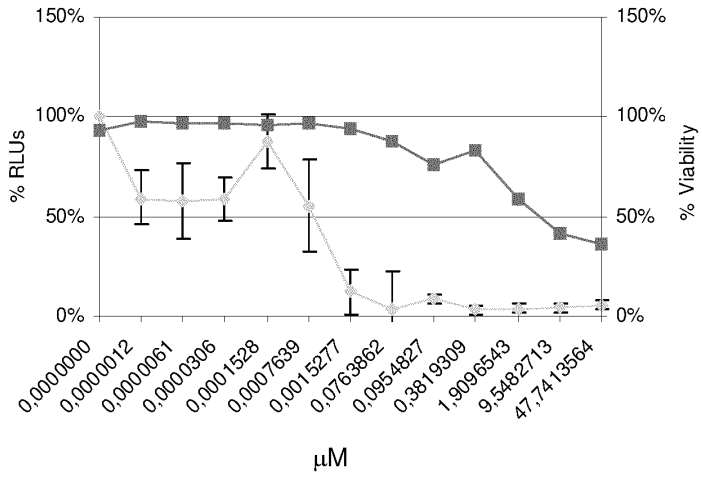


Figure 4B

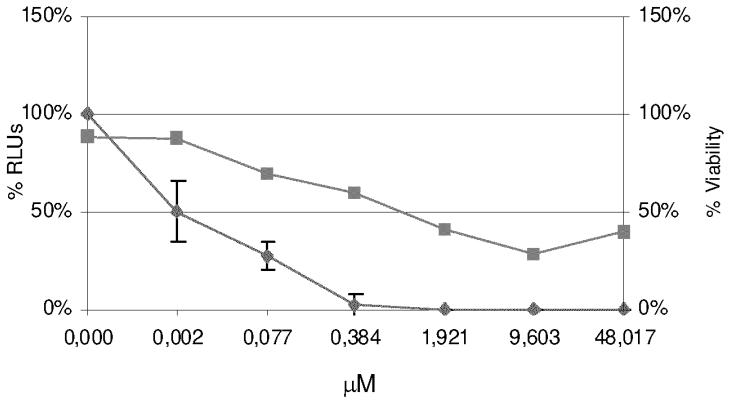


Figure 5A

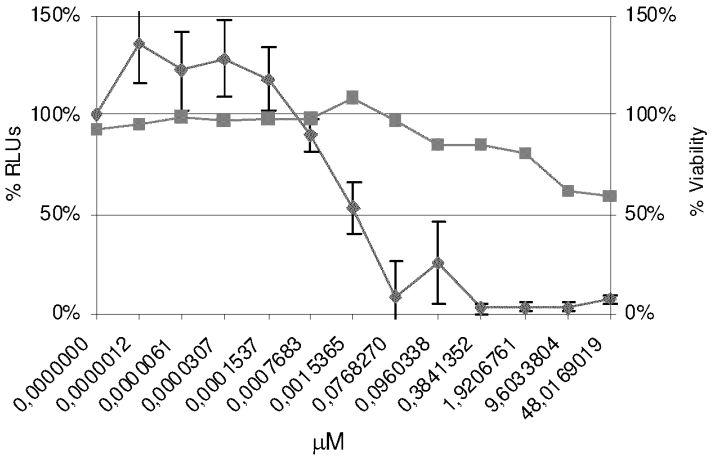


Figure 5B

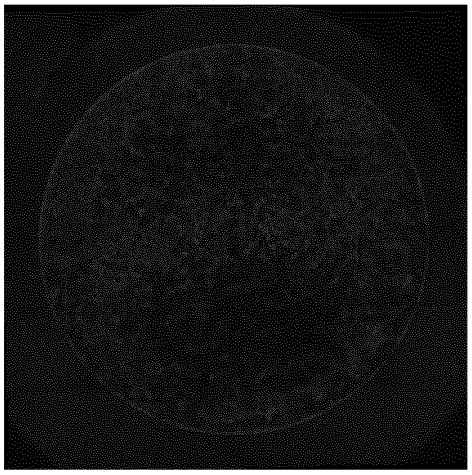


Figure 6a

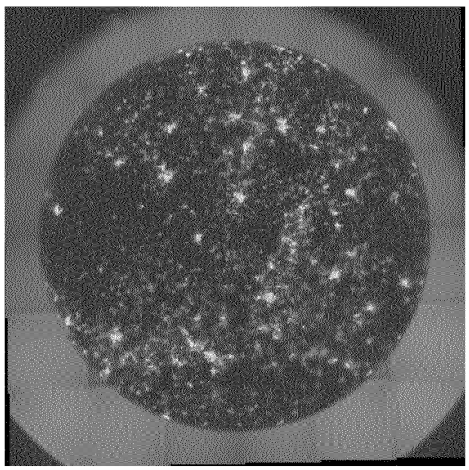


Figure 6b

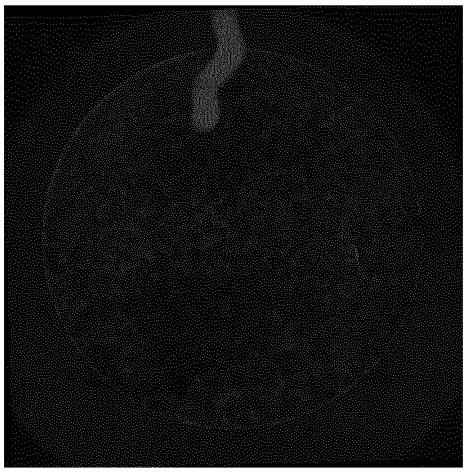


Figure 7a

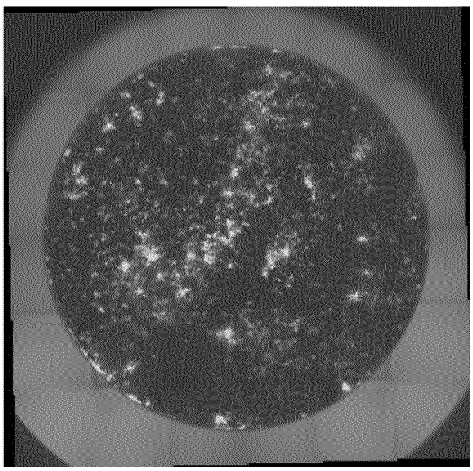


Figure 7b

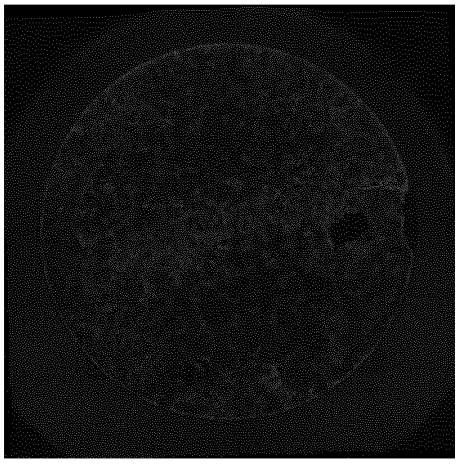


Figure 8a

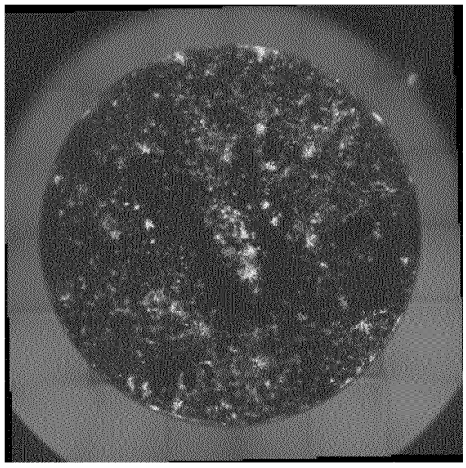


Figure 8b

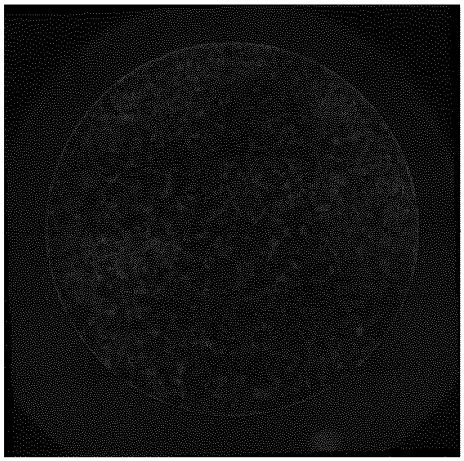


Figure 9a

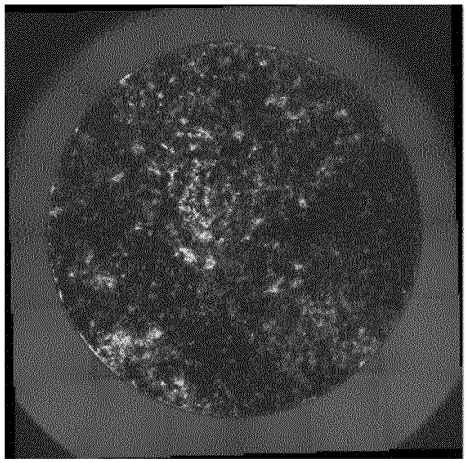


Figure 9b

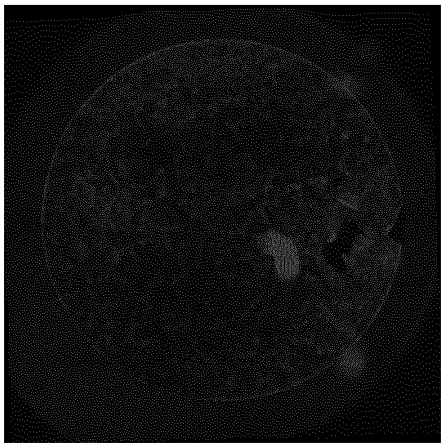


Figure 10a

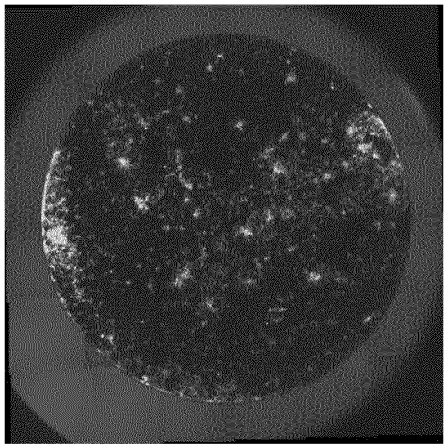


Figure 10b

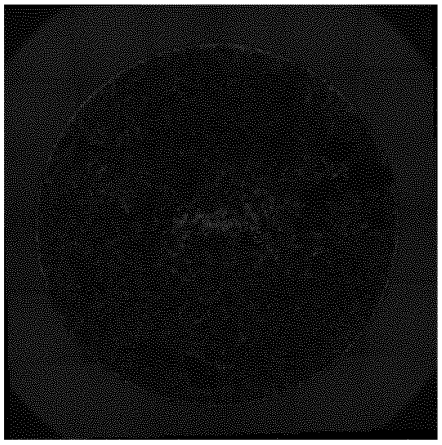


Figure 11a

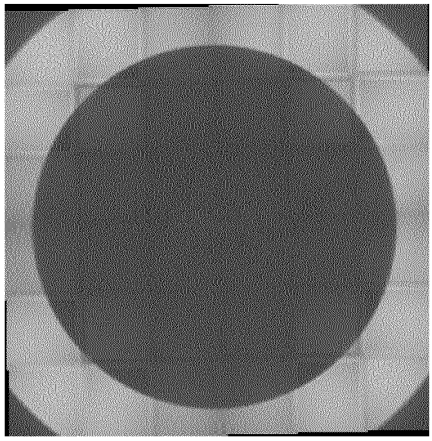


Figure 11b

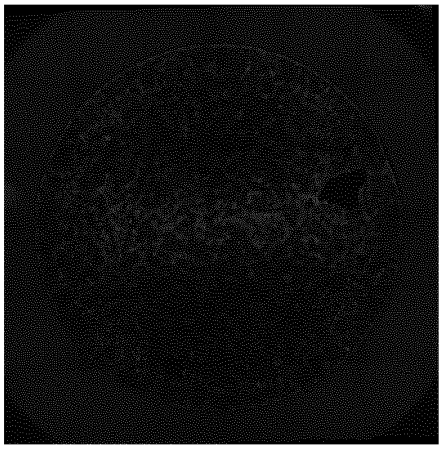


Figure 12a

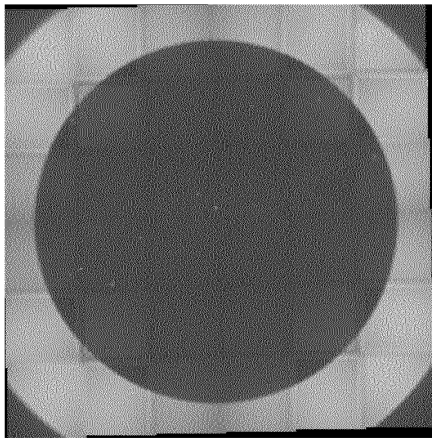


Figure 12b

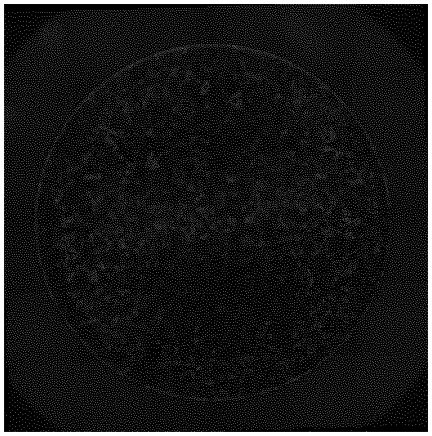


Figure 13a

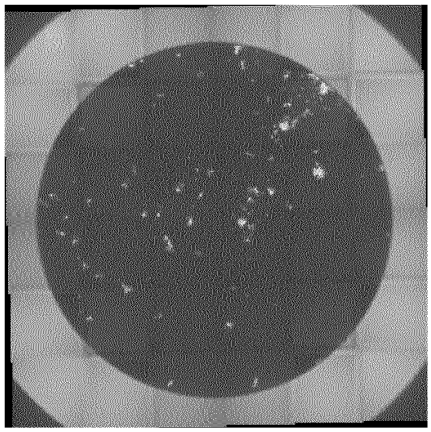


Figure 13b

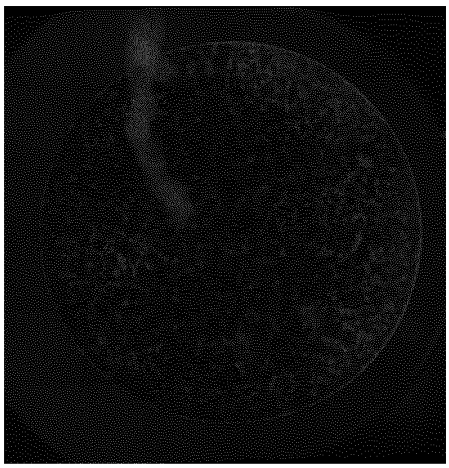


Figure 14a

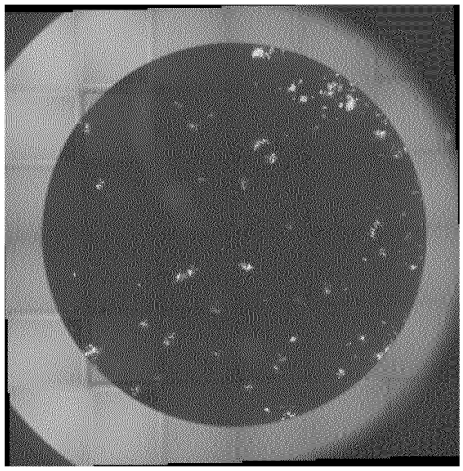


Figure 14b

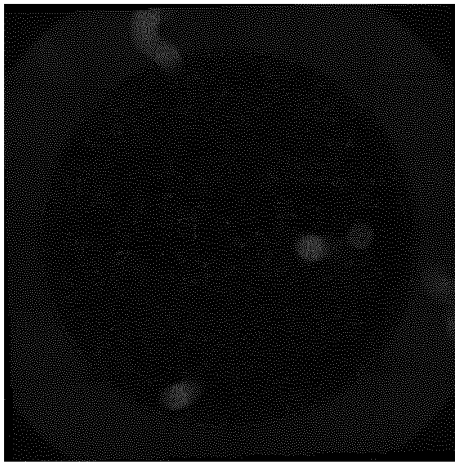


Figure 15a

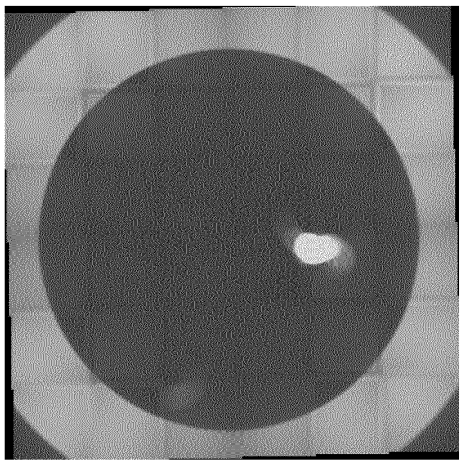


Figure 15b

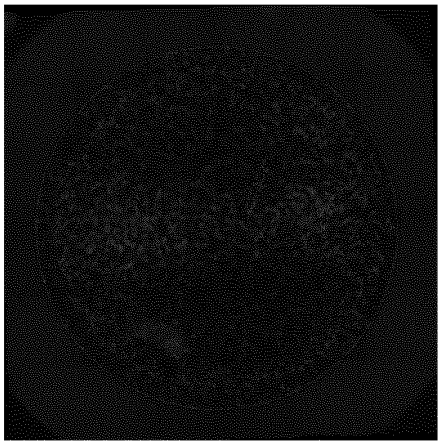


Figure 16a

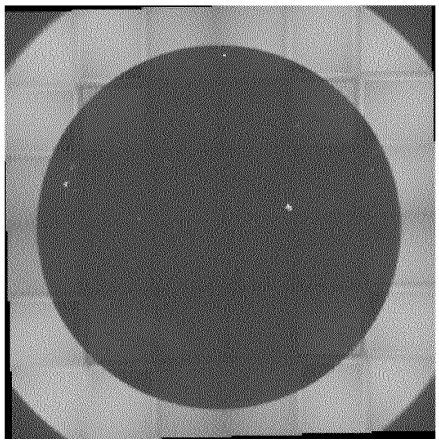


Figure 16b

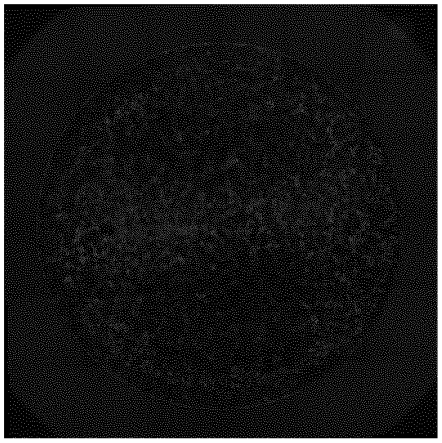


Figure 17a

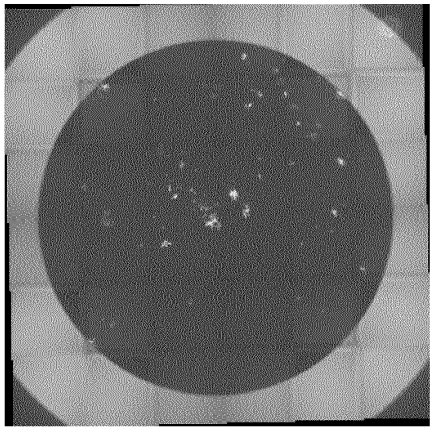


Figure 17b

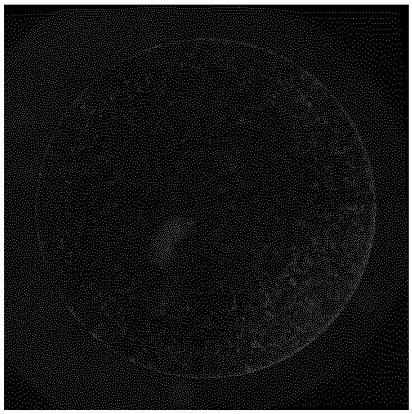


Figure 18a

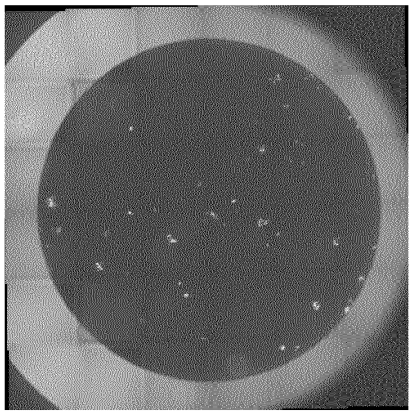


Figure 18b

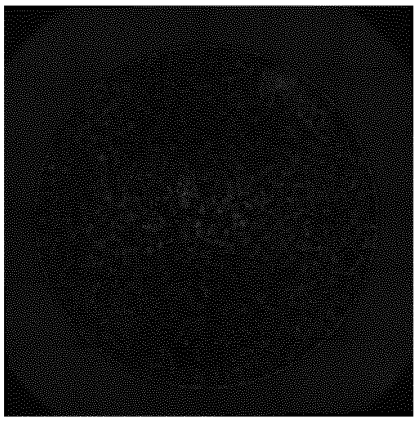


Figure 19a

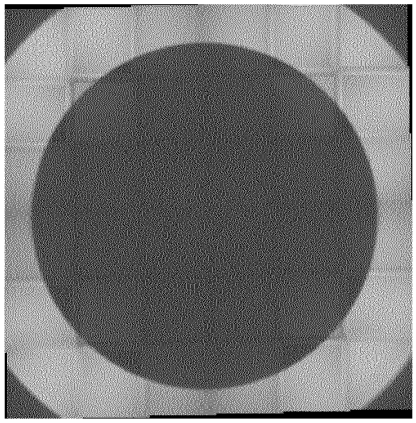


Figure 19b

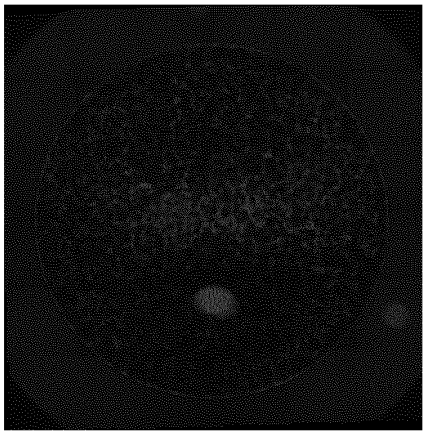


Figure 20a

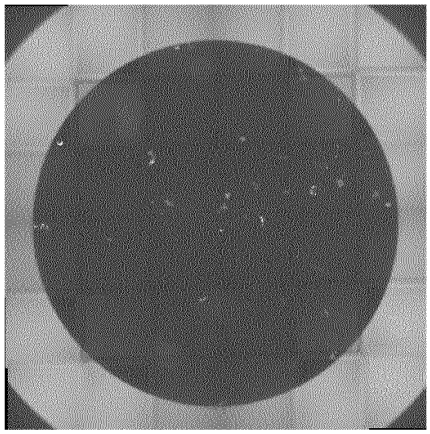


Figure 20b

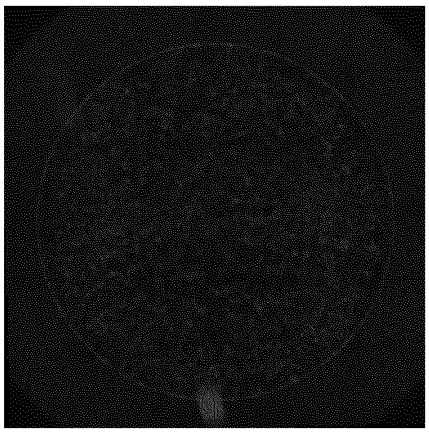


Figure 21a

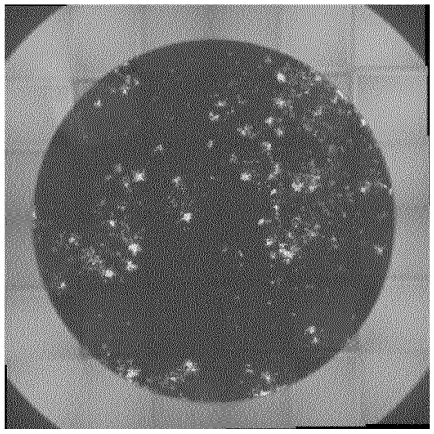


Figure 21b

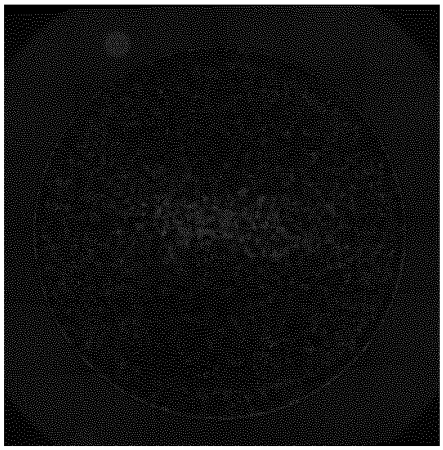


Figure 22a

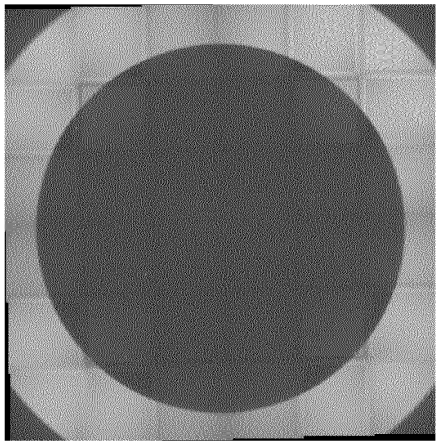


Figure 22b

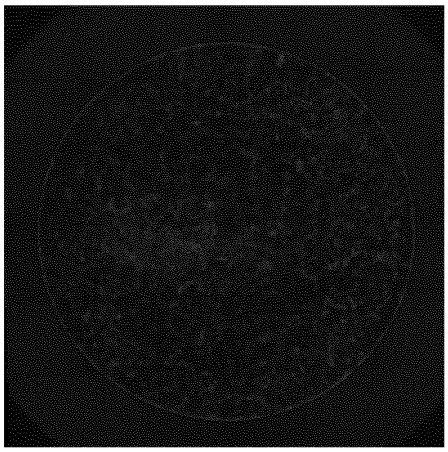


Figure 23a

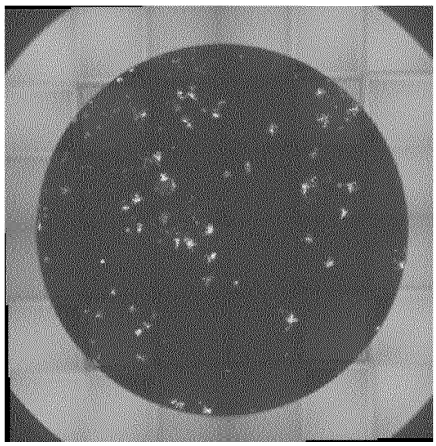


Figure 23b

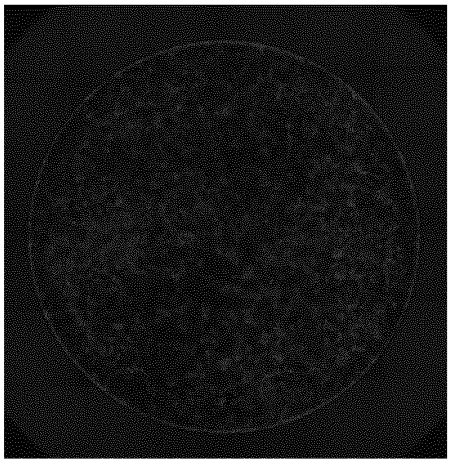


Figure 24a

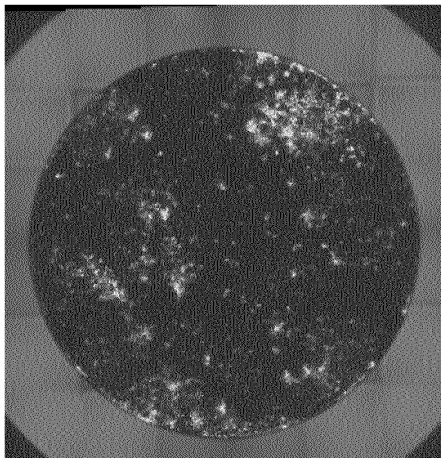


Figure 24b

5

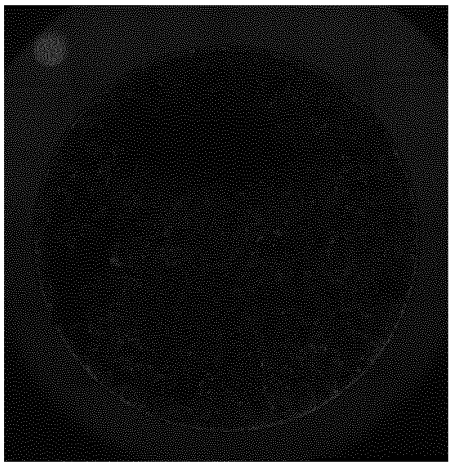


Figure 25a

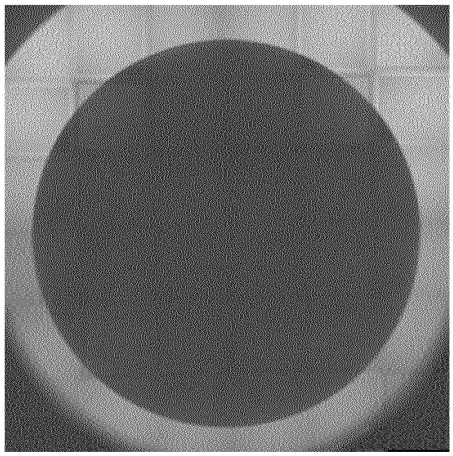


Figure 25b

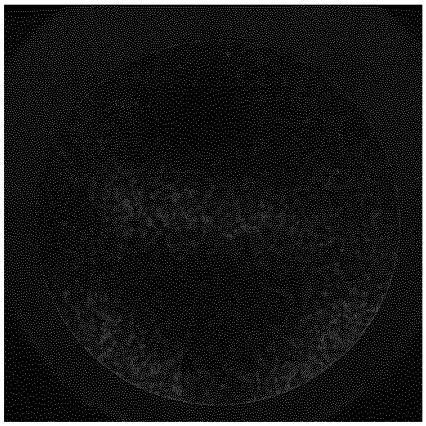


Figure 26a

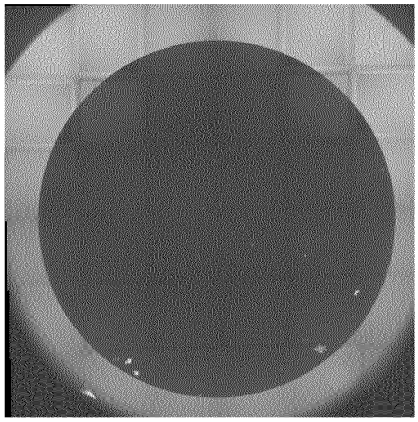


Figure 26b

5

NOT SHOWN

Figure 27a

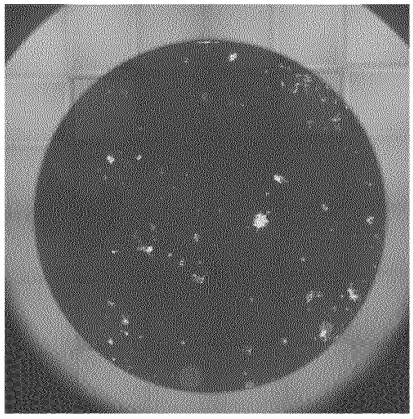


Figure 27b

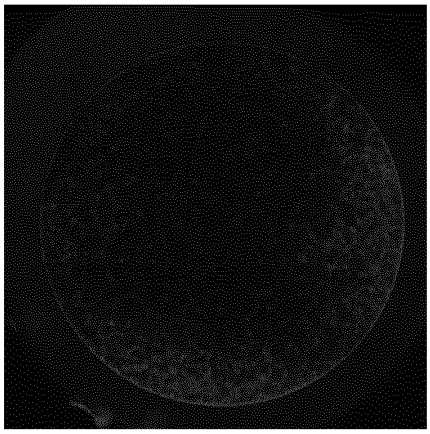


Figure 28a

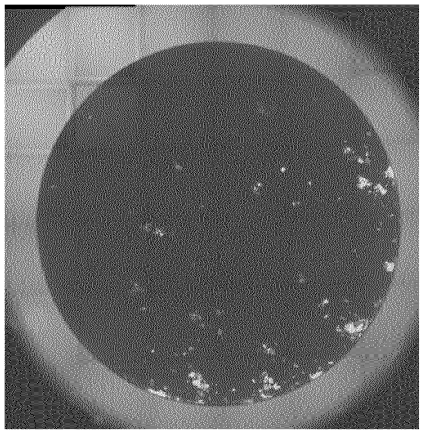


Figure 28b

5

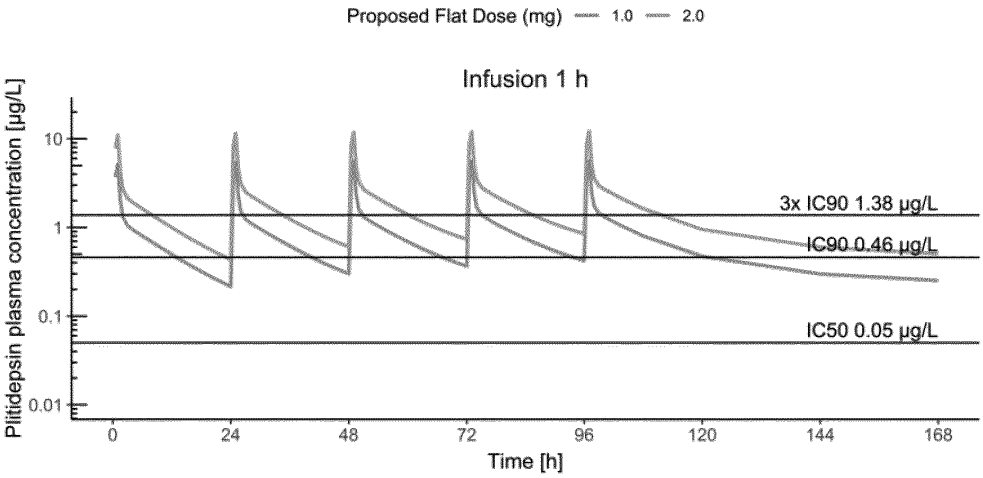


Figure 29

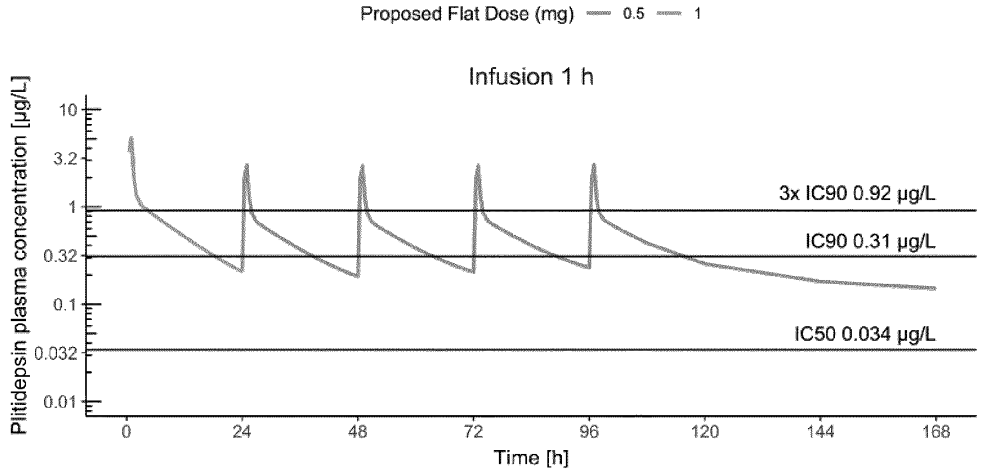


Figure 30

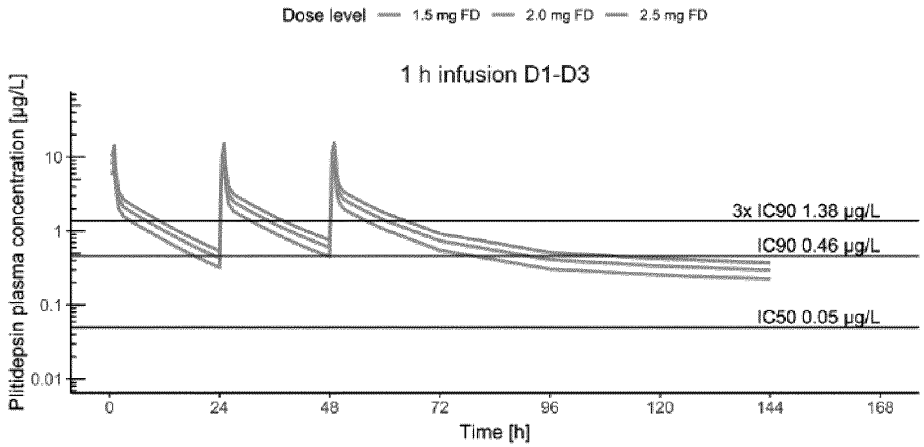

Dose level 1.5 mg FD 2.0 mg FD 2.5 mg FD
1 h infusion D1-D3
Plitidepsin plasma concentration [µg/L]
10
1
0.1
0.01
3x IC90 1.38 µg/L
IC90 0.46 µg/L
IC50 0.05 µg/L
0
24
48
72
96
120
144
168
Time [h]

Figure 31

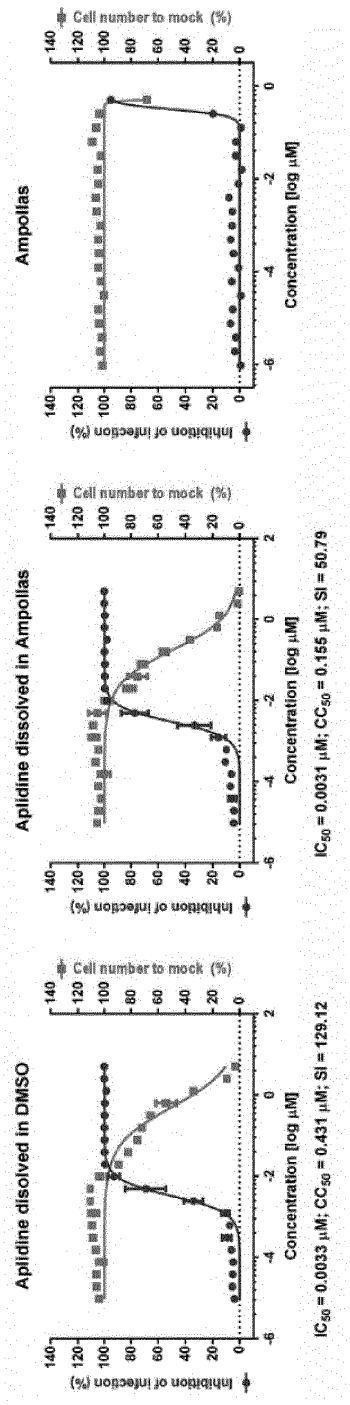

Ampollas
Aplidine dissolved in Ampollas
Aplidine disolved in DMSO
Cell number to mock (%)
Inhibition of infection (%)
Concentration [log µM]
IC50 = 0.0031 µM; CC50 = 0.155 µM; SI = 50.79
IC50 = 0.0033 µM; CC50 = 0.431 µM; SI = 129.12

Figure 32A

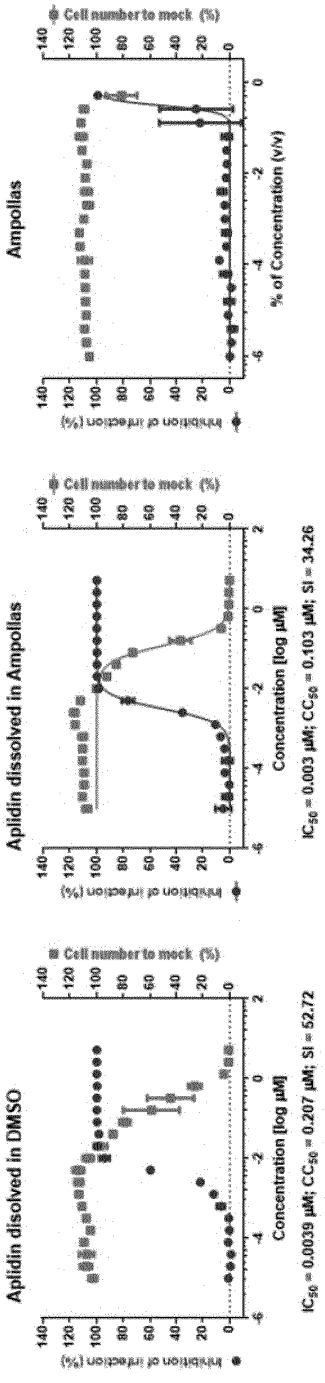

Ampollas
Cell number to mock (%)
Inhibition of infection (%)
% of Concentration (v/v)
Aplidin dissolved in Ampollas
Concentration [log µM]
IC50 = 0.003 µM; CC50 = 0.103 µM; SI = 34.26
Aplidin disolved in DMSO
IC50 = 0.0039 µM; CC50 = 0.207 µM; SI = 52.72

Figure 32 B

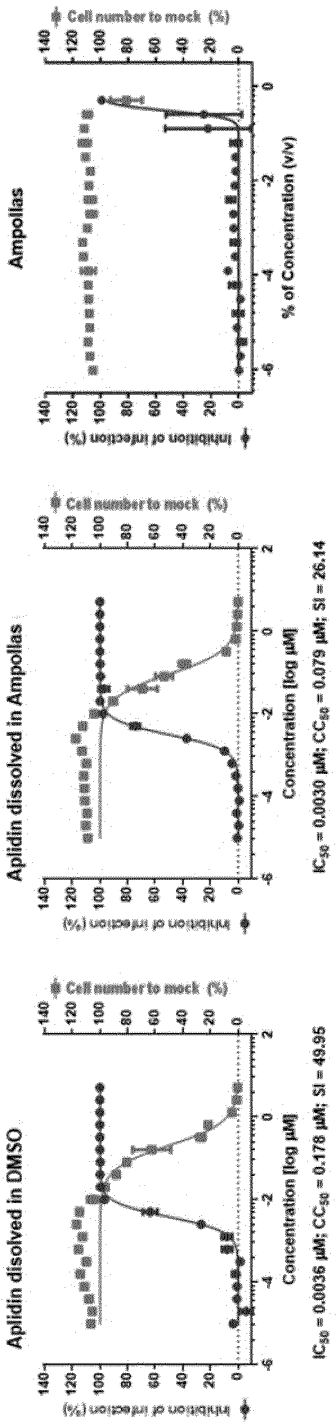

Aplidin disolved in DMSO
Aplidin dissolved in Ampollas
Ampollas
Cell number to mock (%)
Inhibition of infection (%)
Concentration [log µM]
% of Concentration (v/v)
IC50 = 0.0036 µM; CC50 = 0.178 µM; SI = 49.95
IC50 = 0.0030 µM; CC50 = 0.079 µM; SI = 26.14

Figure 32 C

5

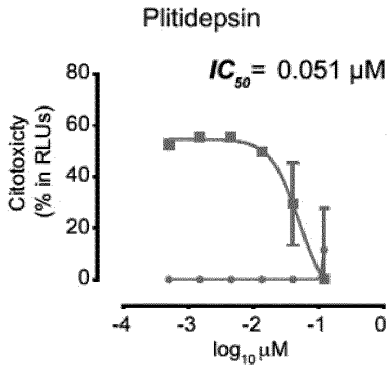


Figure 33

5

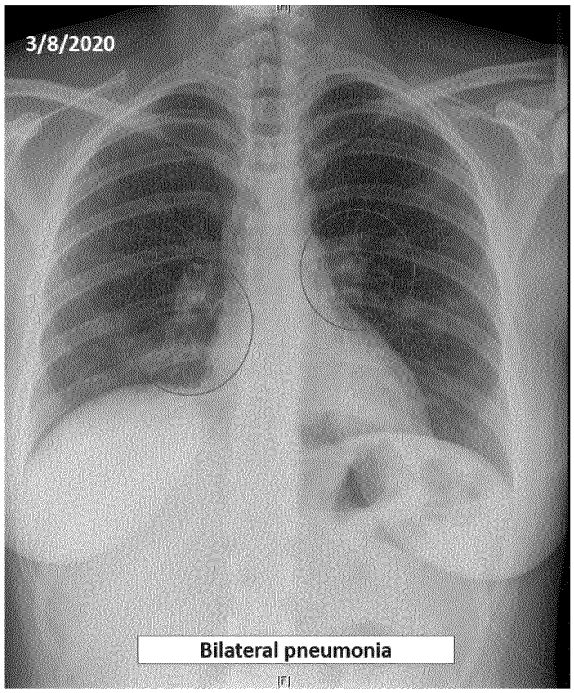


Figure 34a

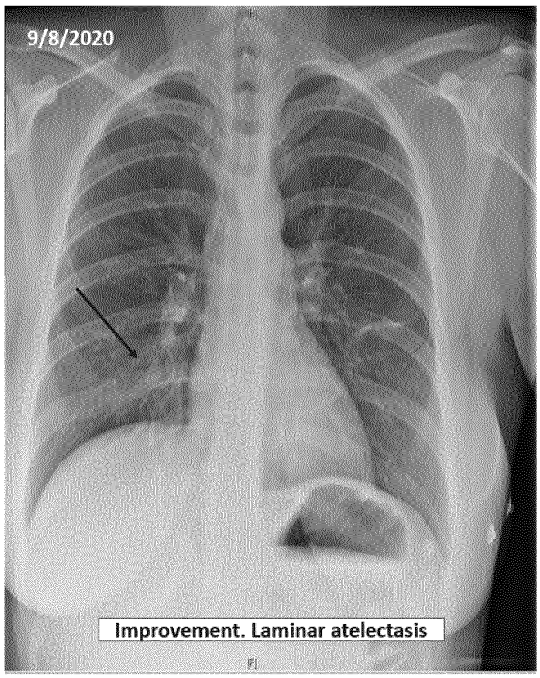


Figure 34b

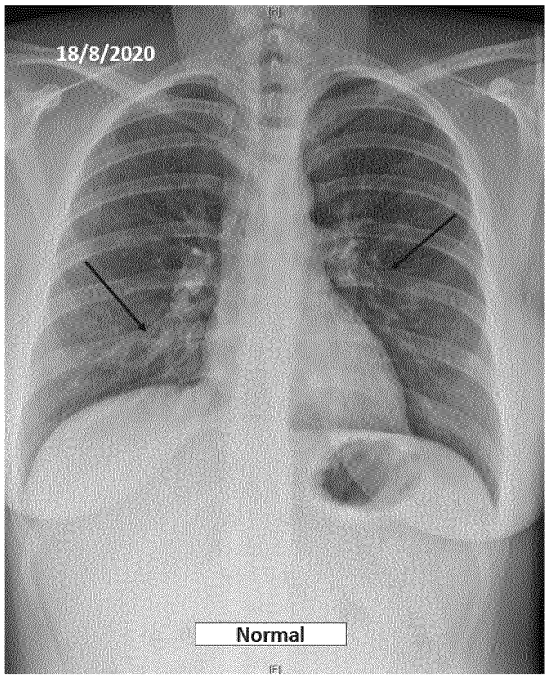


Figure 34c

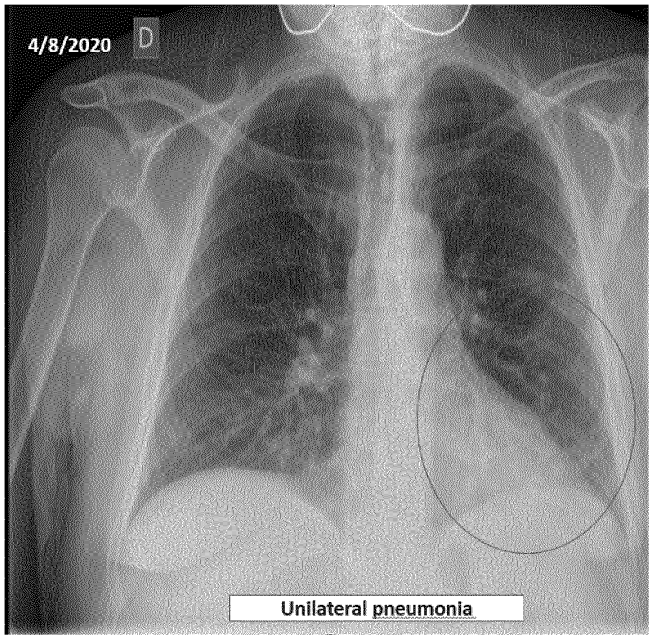


Figure 35a

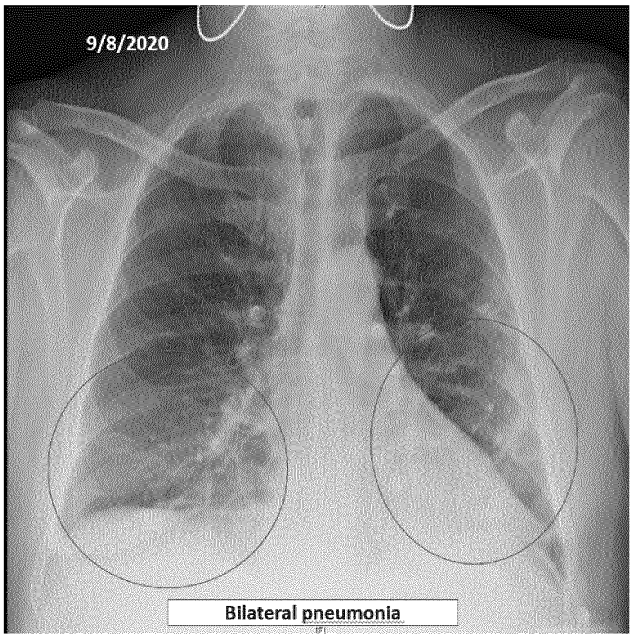


Figure 35b

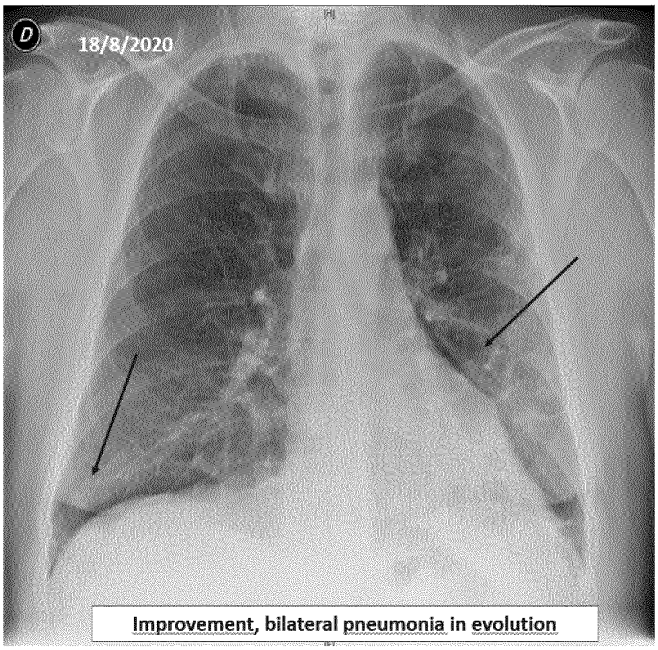


Figure 35c

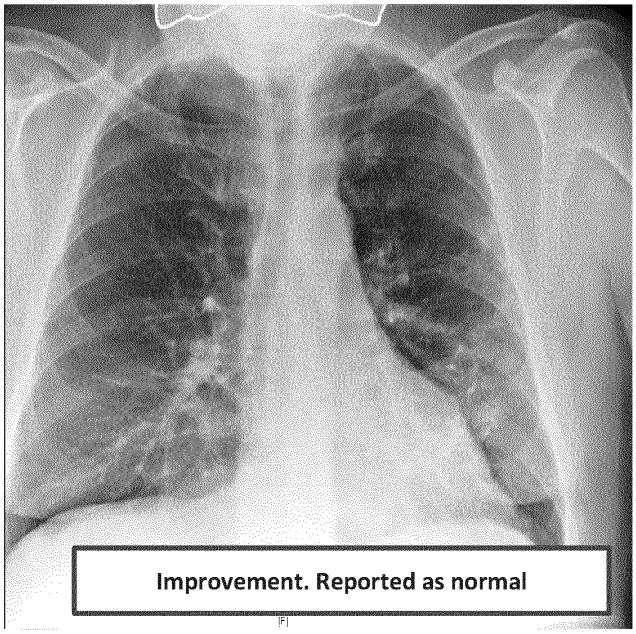


Figure 35d

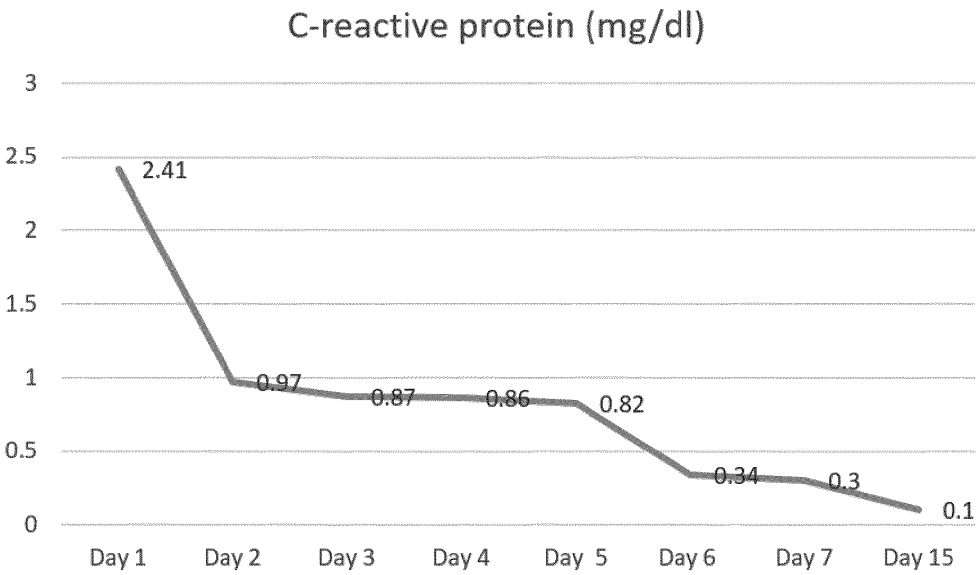

C-reactive protein (mg/dl)
3
2.5
2
1.5
1
0.5
0
2.41
0.97
0.87
0.86
0.82
0.34
0.3
0.1
Day 1
Day 2
Day 3
Day 4
Day 5
Day 6
Day 7
Day 15

Figure 36a

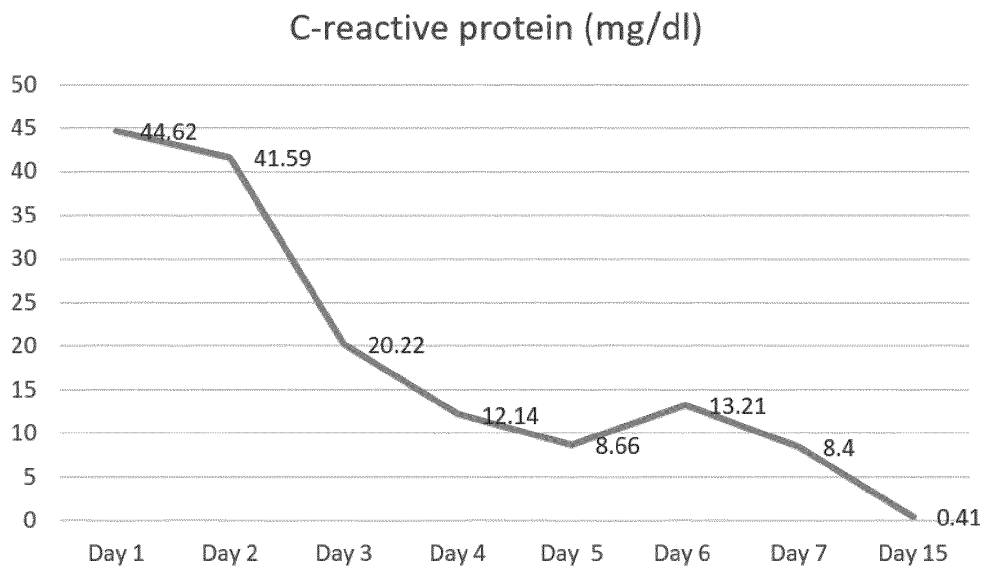


Figure 36b

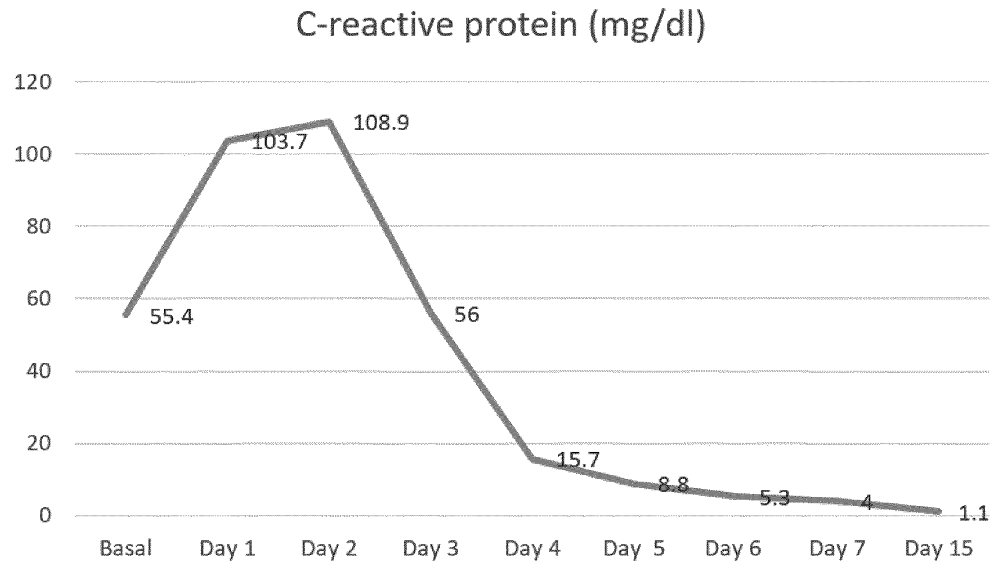


Figure 36c

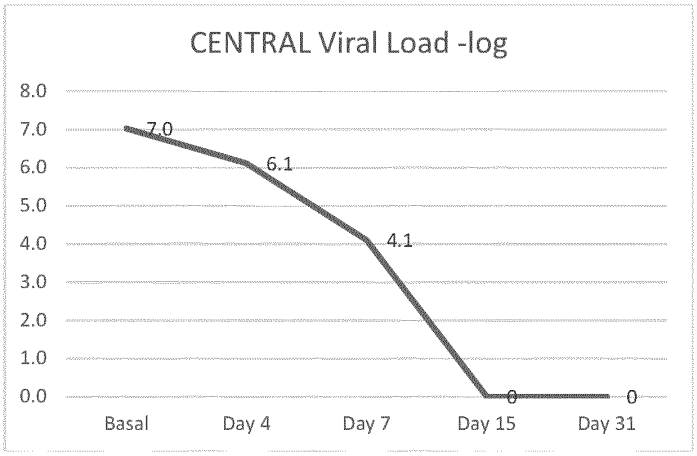


Figure 37a

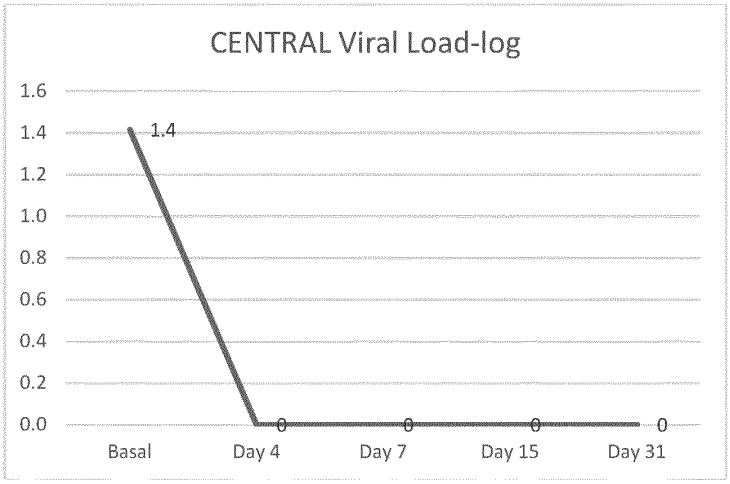


Figure 37b

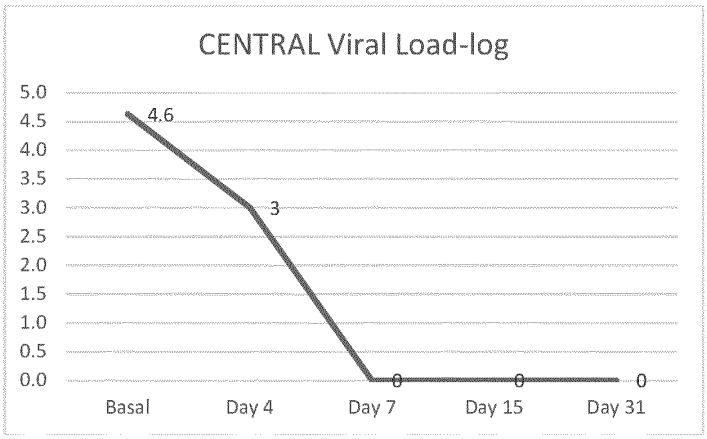


Figure 37c

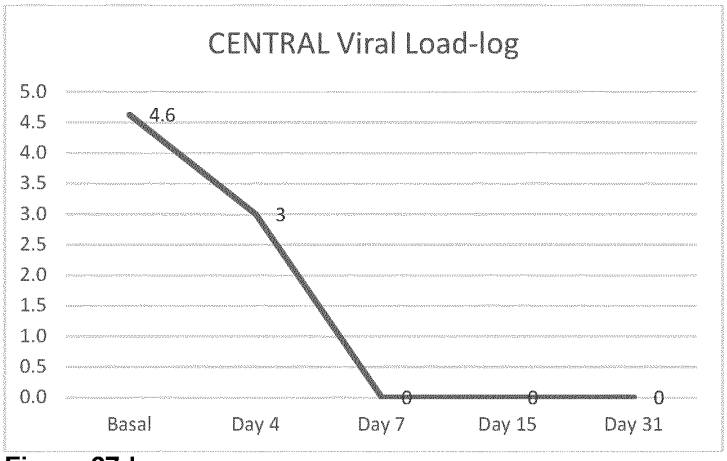


Figure 37d

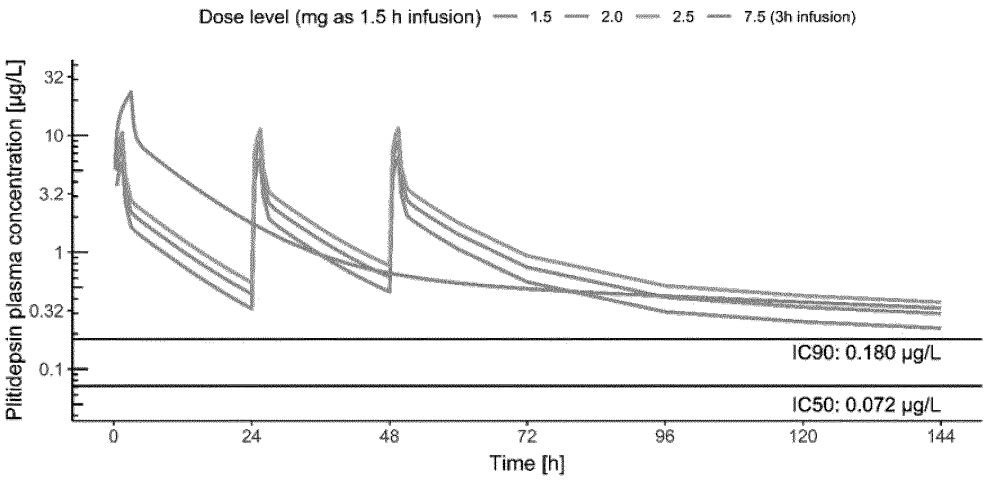

Dose level (mg as 1.5 h infusion)
1.5
2.0
2.5
7.5 (3h infusion)
Plitidepsin plasma concentration [µg/L]
32
10
3.2
1
0.32
0.1
IC90: 0.180 µg/L
IC50: 0.072 µg/L
0
24
48
72
96
120
144
Time [h]

Figure 38