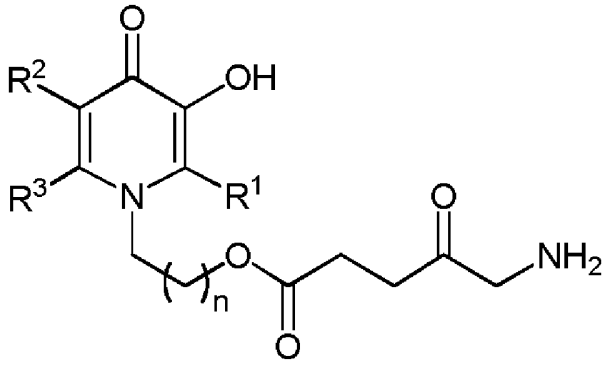
ABSTRACT

"PYRIDINONE COMPOUNDS FOR USE IN PHOTODYNAMIC THERAPY"

A compound which is a compound of formula (I) or any salt thereof: wherein R1 is a Ci-C6 alkyl group, R2 is H or a Ci-C6 alkyl group, R3 is H or a Ci-C6 alkyl group, and n is an integer from 0 to 5.



(I)

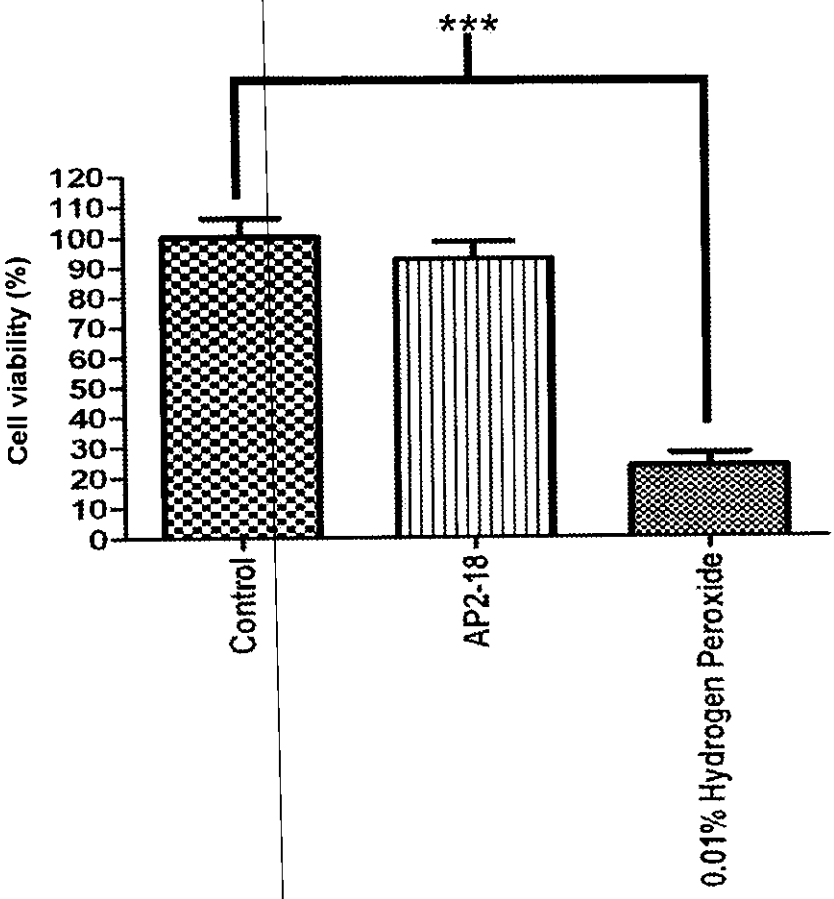


Figure 1

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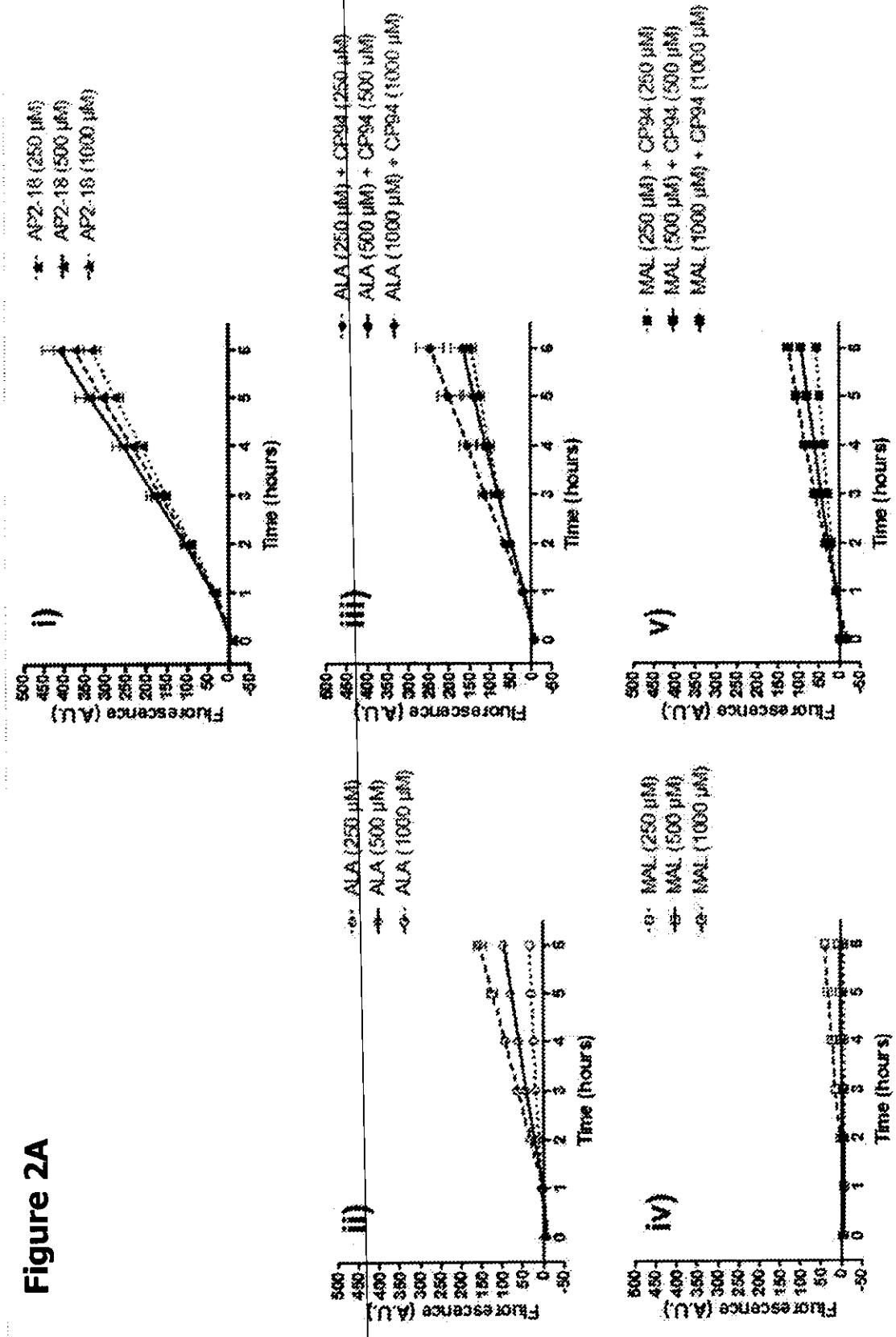

Figure 2A

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AP2-18 (250 µM)

vs	Time (hours) 0	1	2	3	4	5	6
ALA (250 µM)	n.s	n.s	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001
ALA (500 µM)	n.s	n.s	P<0.01	P<0.001	P<0.001	P<0.001	P<0.001
ALA (1000 µM)	n.s	n.s	P<0.05	P<0.001	P<0.001	P<0.001	P<0.001
ALA (250 µM) + CP94 (250 µM)	n.s	n.s	n.s	P<0.001	P<0.001	P<0.001	P<0.001
ALA (500 µM) + CP94 (500 µM)	n.s	n.s	n.s	P<0.01	P<0.001	P<0.001	P<0.001
ALA (1000 µM) + CP94 (1000 µM)	n.s	n.s	n.s	n.s	P<0.05	P<0.01	P<0.001
MAL (250 µM)	n.s	n.s	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001
MAL (500 µM)	n.s	n.s	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001
MAL (1000 µM)	n.s	n.s	P<0.001	P<0.01	P<0.001	P<0.001	P<0.001
MAL (250 µM) + CP94 (250 µM)	n.s	n.s	P<0.01	P<0.001	P<0.001	P<0.001	P<0.001
MAL (500 µM) + CP94 (500 µM)	n.s	n.s	P<0.01	P<0.001	P<0.001	P<0.001	P<0.001
MAL (1000 µM) + CP94 (1000 µM)	n.s	n.s	P<0.05	P<0.001	P<0.001	P<0.001	P<0.001
AP-18 (250 µM)							
AP-18 (500 µM)	n.s	n.s	n.s	n.s	n.s	P<0.01	P<0.001
AP-18 (1000 µM)	n.s	n.s	n.s	n.s	n.s	n.s	n.s

AP2-18 (500 µM)

vs	Time(hours) 0	1	2	3	4	5	6
ALA (250 µM)	n.s	n.s	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001
ALA (500 µM)	n.s	n.s	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001
ALA (1000 µM)	n.s	n.s	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001
ALA (250 µM) + CP94 (250 µM)	n.s	n.s	P<0.05	P<0.001	P<0.001	P<0.001	P<0.001
ALA (500 µM) + CP94 (500 µM)	n.s	n.s	P<0.05	P<0.001	P<0.001	P<0.001	P<0.001
ALA (1000 µM) + CP94 (1000 µM)	n.s	n.s	n.s	P<0.01	P<0.001	P<0.001	P<0.001
MAL (250 µM)	n.s	n.s	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001
MAL (500 µM)	n.s	n.s	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001
MAL (1000 µM)	n.s	n.s	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001
MAL (250 µM) + CP94 (250 µM)	n.s	n.s	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001
MAL (500 µM) + CP94 (500 µM)	n.s	n.s	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001
MAL (1000 µM) + CP94 (1000 µM)	n.s	n.s	P<0.01	P<0.001	P<0.001	P<0.001	P<0.001
AP-18 (250 µM)	n.s	n.s	n.s	n.s	n.s	P<0.01	P<0.001
AP-18 (500 µM)							
AP-18 (1000 µM)	n.s	n.s	n.s	n.s	n.s	n.s	n.s

AP2-18 (1000 µM)

vs	Time(hours) 0	1	2	3	4	5	6
ALA (250 µM)	n.s	n.s	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001
ALA (500 µM)	n.s	n.s	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001
ALA (1000 µM)	n.s	n.s	P<0.01	P<0.001	P<0.001	P<0.001	P<0.001
ALA (250 µM) + CP94 (250 µM)	n.s	n.s	n.s	P<0.001	P<0.001	P<0.001	P<0.001
ALA (500 µM) + CP94 (500 µM)	n.s	n.s	n.s	P<0.001	P<0.001	P<0.001	P<0.001
ALA (1000 µM) + CP94 (1000 µM)	n.s	n.s	n.s	n.s	P<0.001	P<0.001	P<0.001
MAL (250 µM)	n.s	n.s	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001
MAL (500 µM)	n.s	n.s	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001
MAL (1000 µM)	n.s	n.s	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001
MAL (250 µM) + CP94 (250 µM)	n.s	n.s	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001
MAL (500 µM) + CP94 (500 µM)	n.s	n.s	P<0.01	P<0.001	P<0.001	P<0.001	P<0.001
MAL (1000 µM) + CP94 (1000 µM)	n.s	n.s	P<0.01	P<0.001	P<0.001	P<0.001	P<0.001
AP-18 (250 µM)	n.s	n.s	n.s	n.s	n.s	n.s	n.s
AP-18 (500 µM)	n.s	n.s	n.s	n.s	n.s	n.s	n.s
AP-18 (1000 µM)							

P<... Significantly greater than
P>... Significantly less than
n.s No significant difference

Figure 2B

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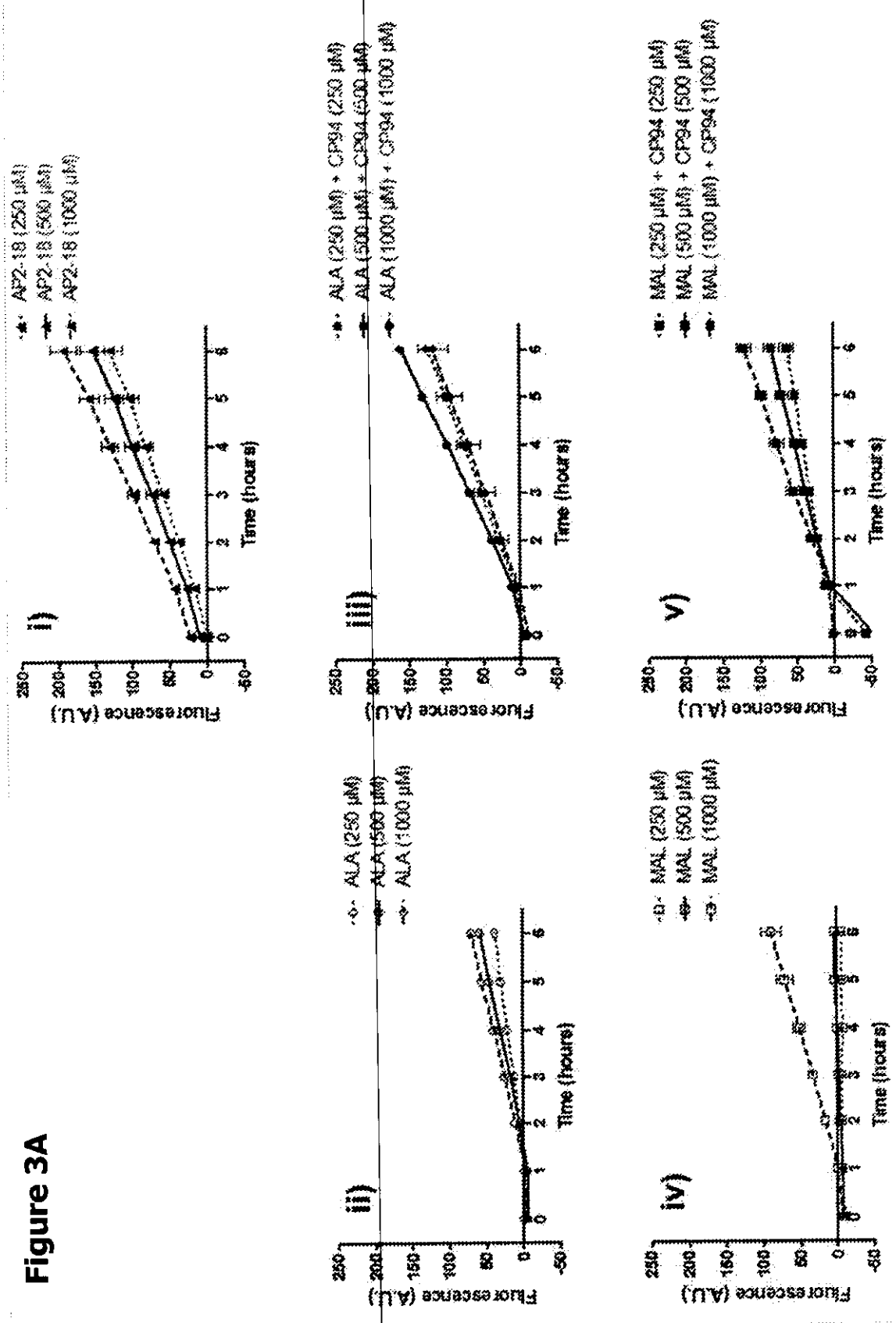

Figure 3A

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AP2-18 (250 µM)

vs	Time (hours) 0	1	2	3	4	5	6
ALA (250 µM)	n.s	n.s	P<0.05	P<0.001	P<0.001	P<0.001	P<0.001
ALA (500 µM)	n.s	n.s	n.s	P<0.01	P<0.001	P<0.001	P<0.001
ALA (1000 µM)	n.s	n.s	n.s	P<0.05	P<0.01	P<0.001	P<0.001
ALA (250 µM) + CP94 (250 µM)	n.s	n.s	n.s	n.s	n.s	n.s	n.s
ALA (500 µM) + CP94 (500 µM)	n.s	n.s	n.s	n.s	n.s	n.s	P<0.05
ALA (1000 µM) + CP94 (1000 µM)	n.s	n.s	n.s	n.s	n.s	n.s	n.s
MAL (250 µM)	n.s	n.s	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001
MAL (500 µM)	n.s	n.s	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001
MAL (1000 µM)	n.s	n.s	n.s	n.s	n.s	P<0.05	P<0.01
MAL (250 µM) + CP94 (250 µM)	P<0.001	n.s	n.s	n.s	P<0.001	P<0.001	P<0.001
MAL (500 µM) + CP94 (500 µM)	P<0.001	n.s	n.s	n.s	P<0.05	P<0.01	P<0.001
MAL (1000 µM) + CP94 (1000 µM)	n.s	n.s	n.s	n.s	n.s	n.s	n.s
AP-18 (250 µM)							
AP-18 (500 µM)	n.s	n.s	n.s	n.s	n.s	n.s	n.s
AP-18 (1000 µM)	n.s	n.s	P<0.01	P<0.001	P<0.001	P<0.001	P<0.001

AP2-18 (500 µM)

vs	Time(hours) 0	1	2	3	4	5	6
ALA (250 µM)	n.s	n.s	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001
ALA (500 µM)	n.s	P<0.05	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001
ALA (1000 µM)	n.s	n.s	P<0.01	P<0.001	P<0.001	P<0.001	P<0.001
ALA (250 µM) + CP94 (250 µM)	n.s	n.s	n.s	n.s	n.s	n.s	n.s
ALA (500 µM) + CP94 (500 µM)	n.s	n.s	n.s	n.s	n.s	n.s	n.s
ALA (1000 µM) + CP94 (1000 µM)	n.s	n.s	n.s	n.s	n.s	n.s	P<0.05
MAL (250 µM)	n.s	P<0.05	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001
MAL (500 µM)	n.s	P<0.05	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001
MAL (1000 µM)	n.s	n.s	P<0.05	P<0.01	P<0.001	P<0.001	P<0.001
MAL (250 µM) + CP94 (250 µM)	P<0.001	n.s	P<0.05	P<0.001	P<0.001	P<0.001	P<0.001
MAL (500 µM) + CP94 (500 µM)	P<0.001	n.s	n.s	P<0.01	P<0.001	P<0.001	P<0.001
MAL (1000 µM) + CP94 (1000 µM)	n.s	n.s	n.s	n.s	n.s	n.s	P<0.05
AP-18 (250 µM)	n.s	n.s	n.s	n.s	n.s	n.s	n.s
AP-18 (500 µM)							
AP-18 (1000 µM)	n.s	n.s	n.s	n.s	P<0.05	P<0.01	P<0.001

AP2-18 (1000 µM)

vs	Time(hours) 0	1	2	3	4	5	6
ALA (250 µM)	n.s	P<0.01	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001
ALA (500 µM)	n.s	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001
ALA (1000 µM)	n.s	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001
ALA (250 µM) + CP94 (250 µM)	n.s	P<0.01	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001
ALA (500 µM) + CP94 (500 µM)	n.s	P<0.05	P<0.05	n.s	P<0.05	n.s	P<0.001
ALA (1000 µM) + CP94 (1000 µM)	P<0.05	P<0.01	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001
MAL (250 µM)	P<0.01	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001
MAL (500 µM)	P<0.05	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001
MAL (1000 µM)	n.s	P<0.01	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001
MAL (250 µM) + CP94 (250 µM)	P<0.001	P<0.05	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001
MAL (500 µM) + CP94 (500 µM)	P<0.001	P<0.01	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001
MAL (1000 µM) + CP94 (1000 µM)	n.s	P<0.05	P<0.01	P<0.01	P<0.001	P<0.001	P<0.001
AP-18 (250 µM)	n.s	n.s	P<0.01	P<0.001	P<0.001	P<0.001	P<0.001
AP-18 (500 µM)	n.s	n.s	n.s	n.s	P<0.05	P<0.01	P<0.001
AP-18 (1000 µM)							

P<.... Significantly greater than
P<.... Significantly less than
n.s No significant difference

Figure 3B

(H. SUBRAMANIAM)
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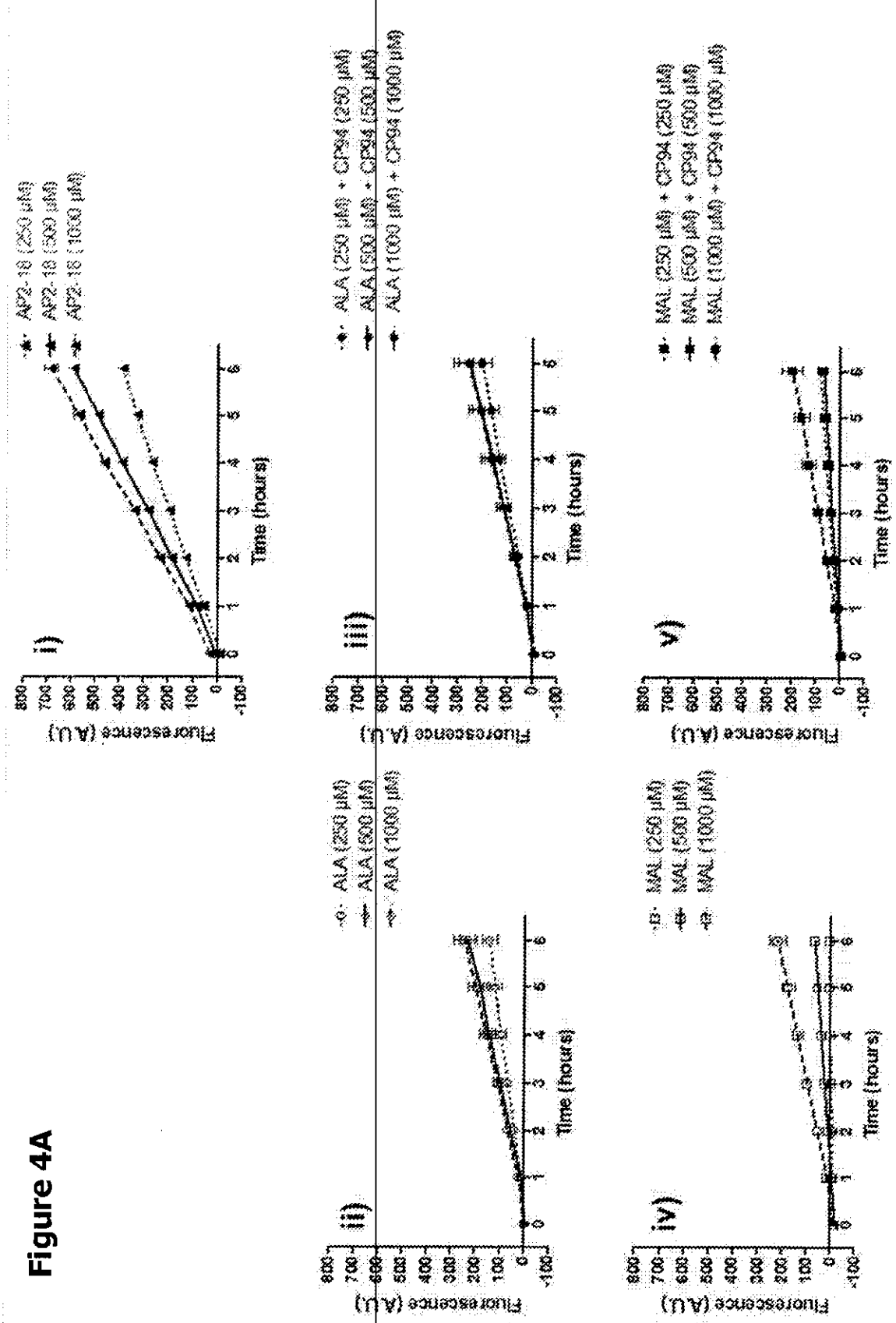

Figure 4A

(H. SUBRAMANIAM)
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AP2-18 (250 µM)

vs	Time (hours) 0	1	2	3	4	5	6
ALA (250 µM)	n.s	n.s	P<0.01	P<0.001	P<0.001	P<0.001	P<0.001
ALA (500 µM)	n.s	n.s	P<0.05	P<0.01	P<0.001	P<0.001	P<0.001
ALA (1000 µM)	n.s	n.s	n.s	P<0.01	P<0.001	P<0.001	P<0.001
ALA (250 µM) + CP94 (250 µM)	n.s	n.s	P<0.05	P<0.01	P<0.001	P<0.001	P<0.001
ALA (500 µM) + CP94 (500 µM)	n.s	n.s	n.s	P<0.05	P<0.001	P<0.001	P<0.001
ALA (1000 µM) + CP94 (1000 µM)	n.s	n.s	n.s	P<0.05	P<0.01	P<0.001	P<0.001
MAL (250 µM)	n.s	n.s	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001
MAL (500 µM)	n.s	n.s	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001
MAL (1000 µM)	n.s	n.s	P<0.05	P<0.01	P<0.001	P<0.001	P<0.001
MAL (250 µM) + CP94 (250 µM)	n.s	n.s	P<0.01	P<0.001	P<0.001	P<0.001	P<0.001
MAL (500 µM) + CP94 (500 µM)	n.s	n.s	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001
MAL (1000 µM) + CP94 (1000 µM)	n.s	n.s	P<0.05	P<0.001	P<0.001	P<0.001	P<0.001
AP-18 (250 µM)							
AP-18 (500 µM)	n.s	n.s	n.s	P<0.01	P<0.001	P<0.001	P<0.001
AP-18 (1000 µM)	n.s	n.s	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001

AP2-18 (500 µM)

vs	Time(hours) 0	1	2	3	4	5	6
ALA (250 µM)	n.s	P<0.05	P<0.01	P<0.001	P<0.001	P<0.001	P<0.001
ALA (500 µM)	n.s	n.s	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001
ALA (1000 µM)	n.s	n.s	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001
ALA (250 µM) + CP94 (250 µM)	n.s	n.s	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001
ALA (500 µM) + CP94 (500 µM)	n.s	n.s	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001
ALA (1000 µM) + CP94 (1000 µM)	n.s	n.s	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001
MAL (250 µM)	n.s	P<0.01	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001
MAL (500 µM)	n.s	P<0.05	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001
MAL (1000 µM)	n.s	n.s	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001
MAL (250 µM) + CP94 (250 µM)	n.s	n.s	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001
MAL (500 µM) + CP94 (500 µM)	n.s	P<0.05	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001
MAL (1000 µM) + CP94 (1000 µM)	n.s	n.s	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001
AP-18 (250 µM)	n.s	n.s	n.s	P<0.01	P<0.001	P<0.001	P<0.001
AP-18 (500 µM)							
AP-18 (1000 µM)	n.s	n.s	n.s	n.s	P<0.05	P<0.05	P<0.01

AP2-18 (1000 µM)

vs	Time(hours) 0	1	2	3	4	5	6
ALA (250 µM)	n.s	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001
ALA (500 µM)	n.s	P<0.01	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001
ALA (1000 µM)	n.s	P<0.01	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001
ALA (250 µM) + CP94 (250 µM)	n.s	P<0.01	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001
ALA (500 µM) + CP94 (500 µM)	n.s	P<0.01	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001
ALA (1000 µM) + CP94 (1000 µM)	n.s	P<0.01	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001
MAL (250 µM)	n.s	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001
MAL (500 µM)	n.s	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001
MAL (1000 µM)	n.s	P<0.01	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001
MAL (250 µM) + CP94 (250 µM)	n.s	P<0.01	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001
MAL (500 µM) + CP94 (500 µM)	n.s	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001
MAL (1000 µM) + CP94 (1000 µM)	n.s	P<0.01	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001
AP-18 (250 µM)	n.s	n.s	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001
AP-18 (500 µM)	n.s	n.s	n.s	n.s	P<0.05	P<0.05	P<0.01
AP-18 (1000 µM)							

P<... Significantly greater than
P>... Significantly less than
n.s No significant difference

Figure 4B

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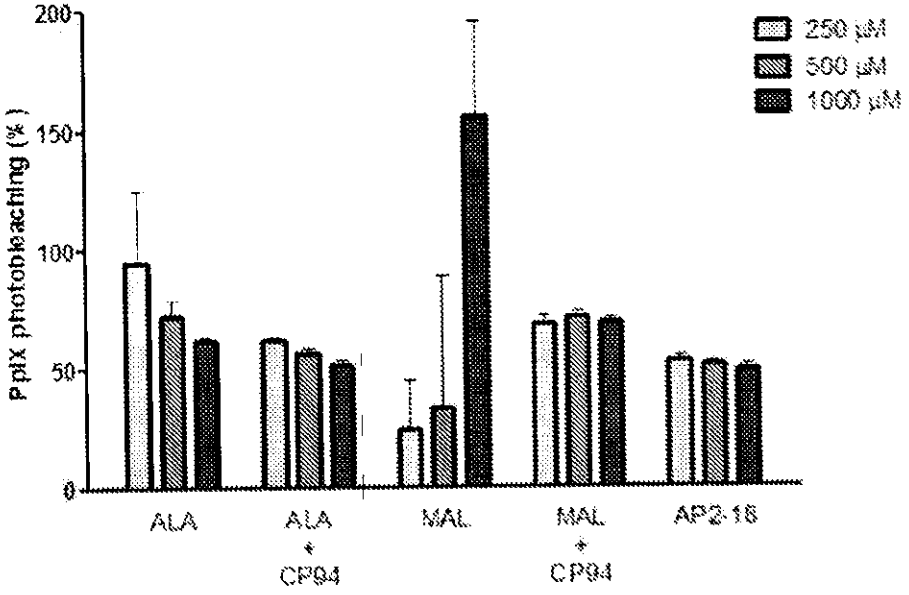

Figure 5A

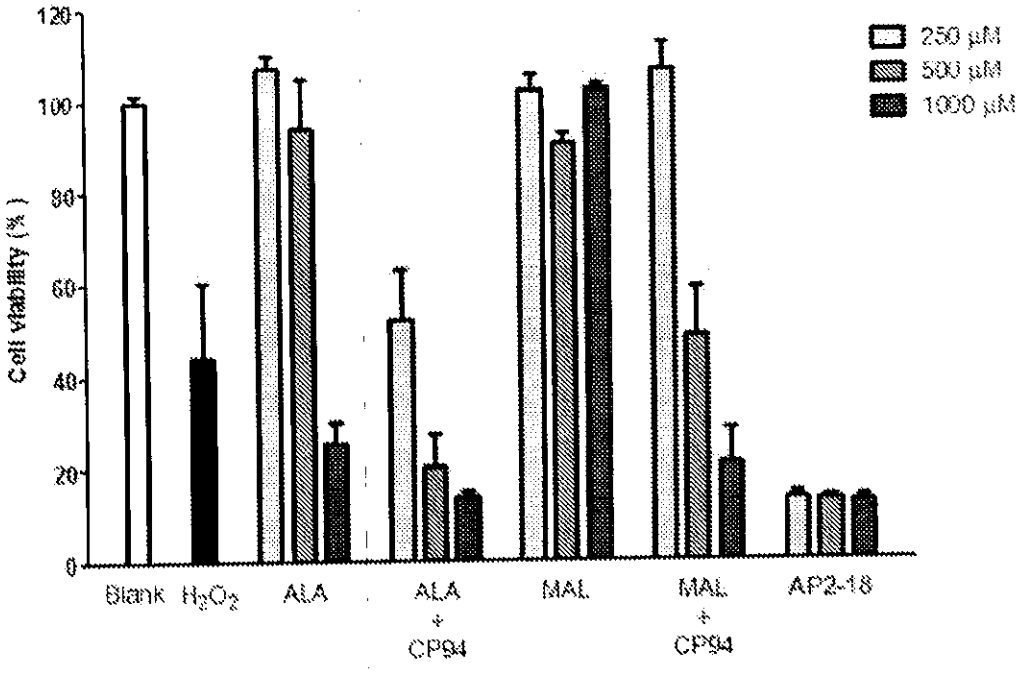

Figure 5B

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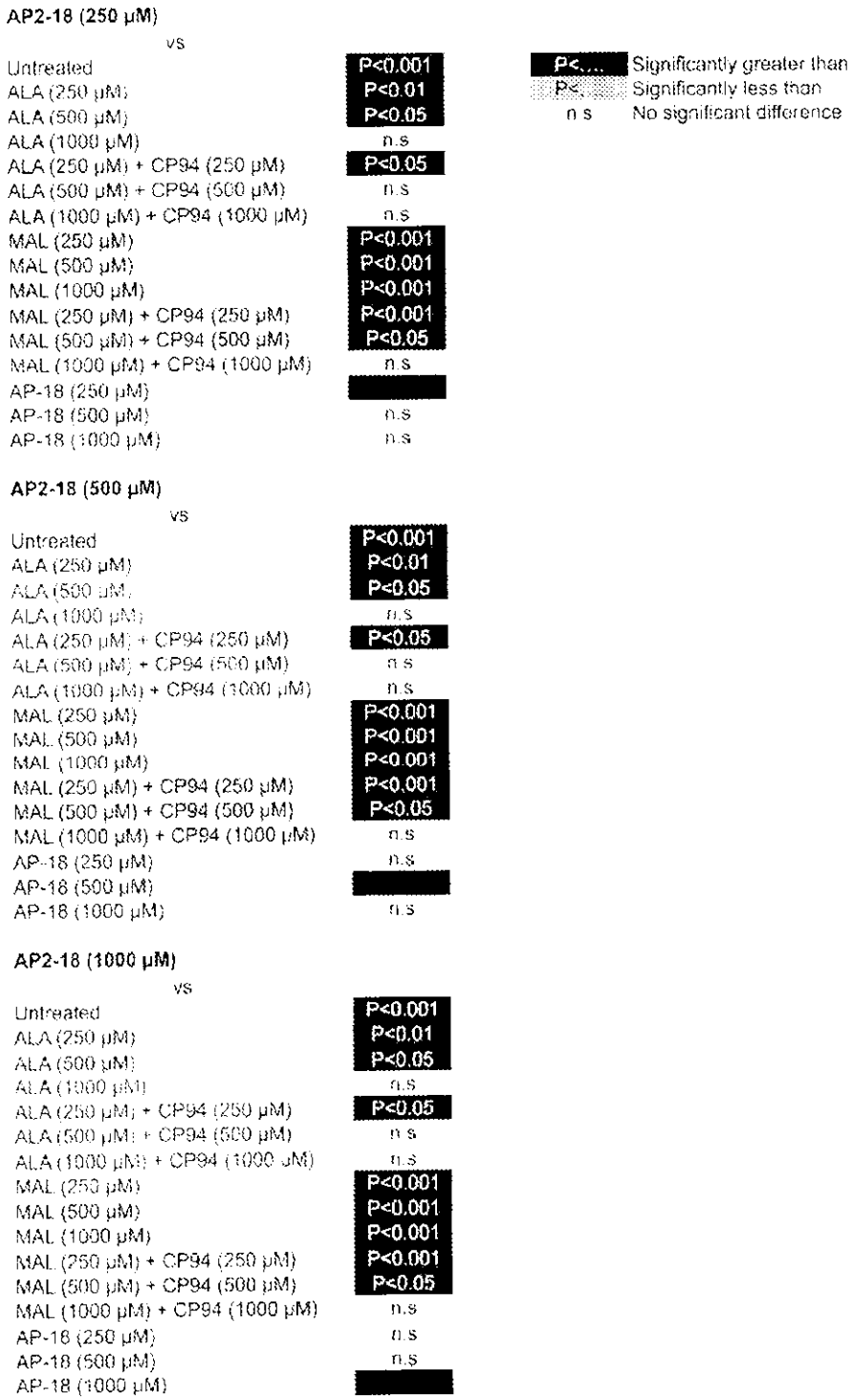

Figure 5C

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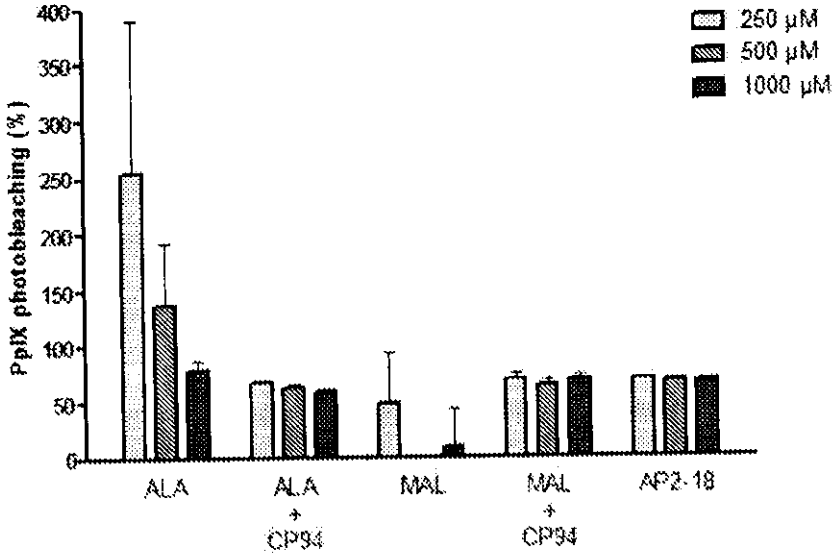

Figure 6A

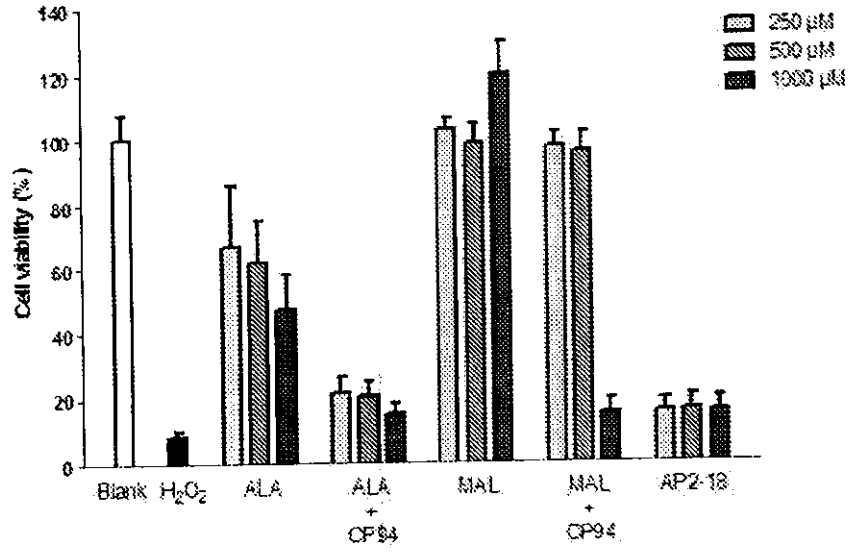

Figure 6B

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AP2-18 (250 µM)

vs

Untreated	P<0.001
ALA (250 µM)	P<0.01
ALA (500 µM)	P<0.05
ALA (1000 µM)	n.s
ALA (250 µM) + CP94 (250 µM)	n.s
ALA (500 µM) + CP94 (500 µM)	n.s
ALA (1000 µM) + CP94 (1000 µM)	n.s
MAL (250 µM)	P<0.001
MAL (500 µM)	P<0.001
MAL (1000 µM)	P<0.001
MAL (250 µM) + CP94 (250 µM)	P<0.001
MAL (500 µM) + CP94 (500 µM)	P<0.001
MAL (1000 µM) + CP94 (1000 µM)	n.s
AP-18 (250 µM)	
AP-18 (500 µM)	n.s
AP-18 (1000 µM)	n.s

AP2-18 (500 µM)

vs

Untreated	P<0.001
ALA (250 µM)	P<0.01
ALA (500 µM)	P<0.05
ALA (1000 µM)	n.s
ALA (250 µM) + CP94 (250 µM)	n.s
ALA (500 µM) + CP94 (500 µM)	n.s
ALA (1000 µM) + CP94 (1000 µM)	n.s
MAL (250 µM)	P<0.001
MAL (500 µM)	P<0.001
MAL (1000 µM)	P<0.001
MAL (250 µM) + CP94 (250 µM)	P<0.001
MAL (500 µM) + CP94 (500 µM)	P<0.001
MAL (1000 µM) + CP94 (1000 µM)	n.s
AP-18 (250 µM)	n.s
AP-18 (500 µM)	
AP-18 (1000 µM)	n.s

AP2-18 (1000 µM)

vs

Untreated	P<0.001
ALA (250 µM)	P<0.01
ALA (500 µM)	P<0.05
ALA (1000 µM)	n.s
ALA (250 µM) + CP94 (250 µM)	n.s
ALA (500 µM) + CP94 (500 µM)	n.s
ALA (1000 µM) + CP94 (1000 µM)	n.s
MAL (250 µM)	P<0.001
MAL (500 µM)	P<0.001
MAL (1000 µM)	P<0.001
MAL (250 µM) + CP94 (250 µM)	P<0.001
MAL (500 µM) + CP94 (500 µM)	P<0.001
MAL (1000 µM) + CP94 (1000 µM)	n.s
AP-18 (250 µM)	n.s
AP-18 (500 µM)	n.s
AP-18 (1000 µM)	

P<....	Significantly greater than
P<....	Significantly less than
n.s	No significant difference

Figure 6C

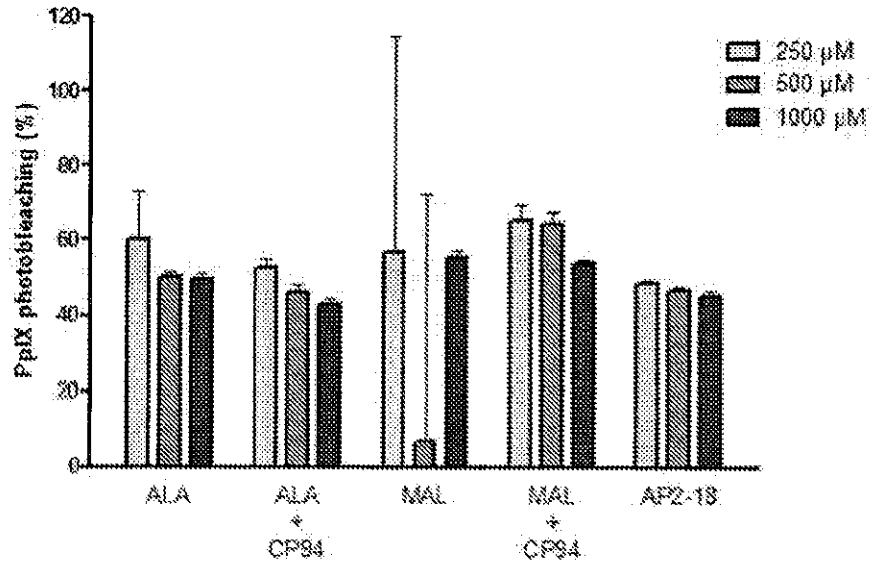

Figure 7A

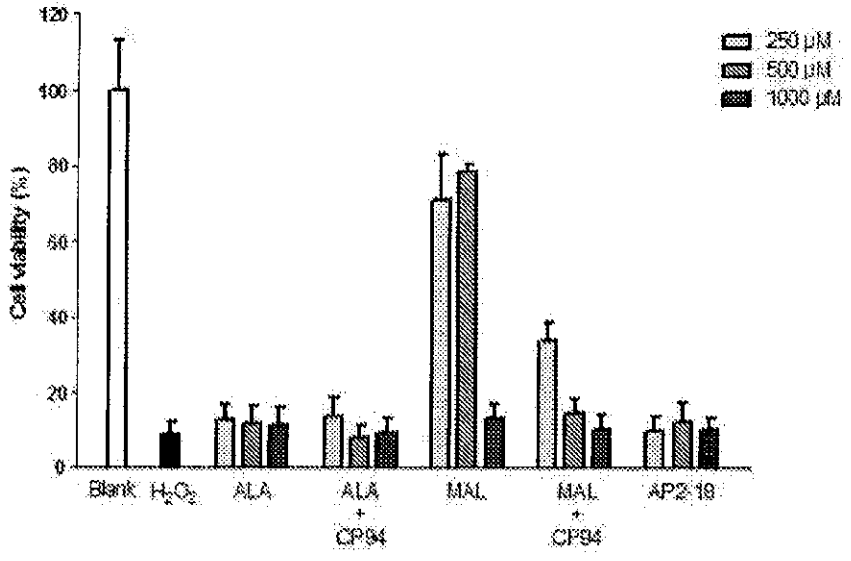

Figure 7B

5

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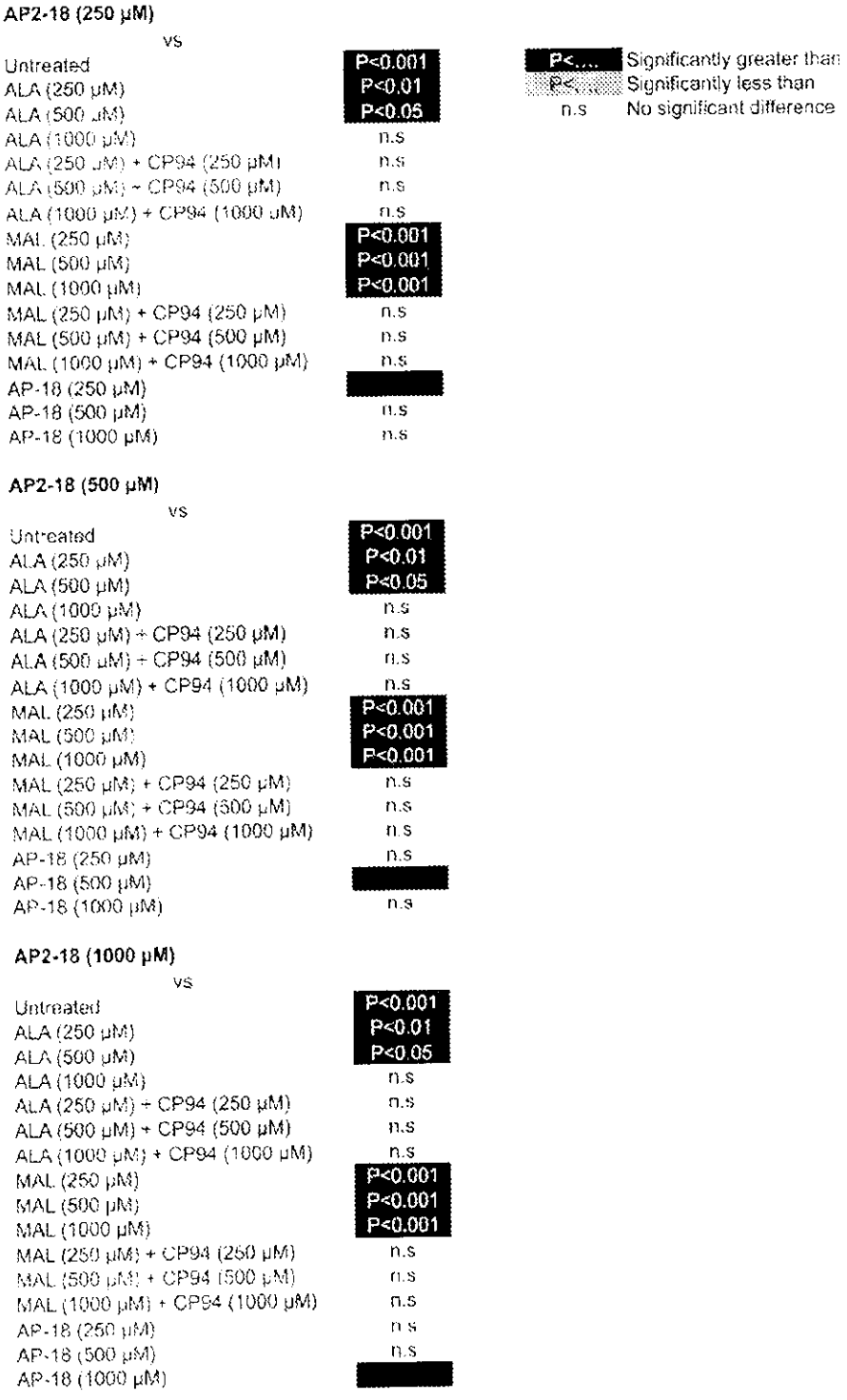

Figure 7C

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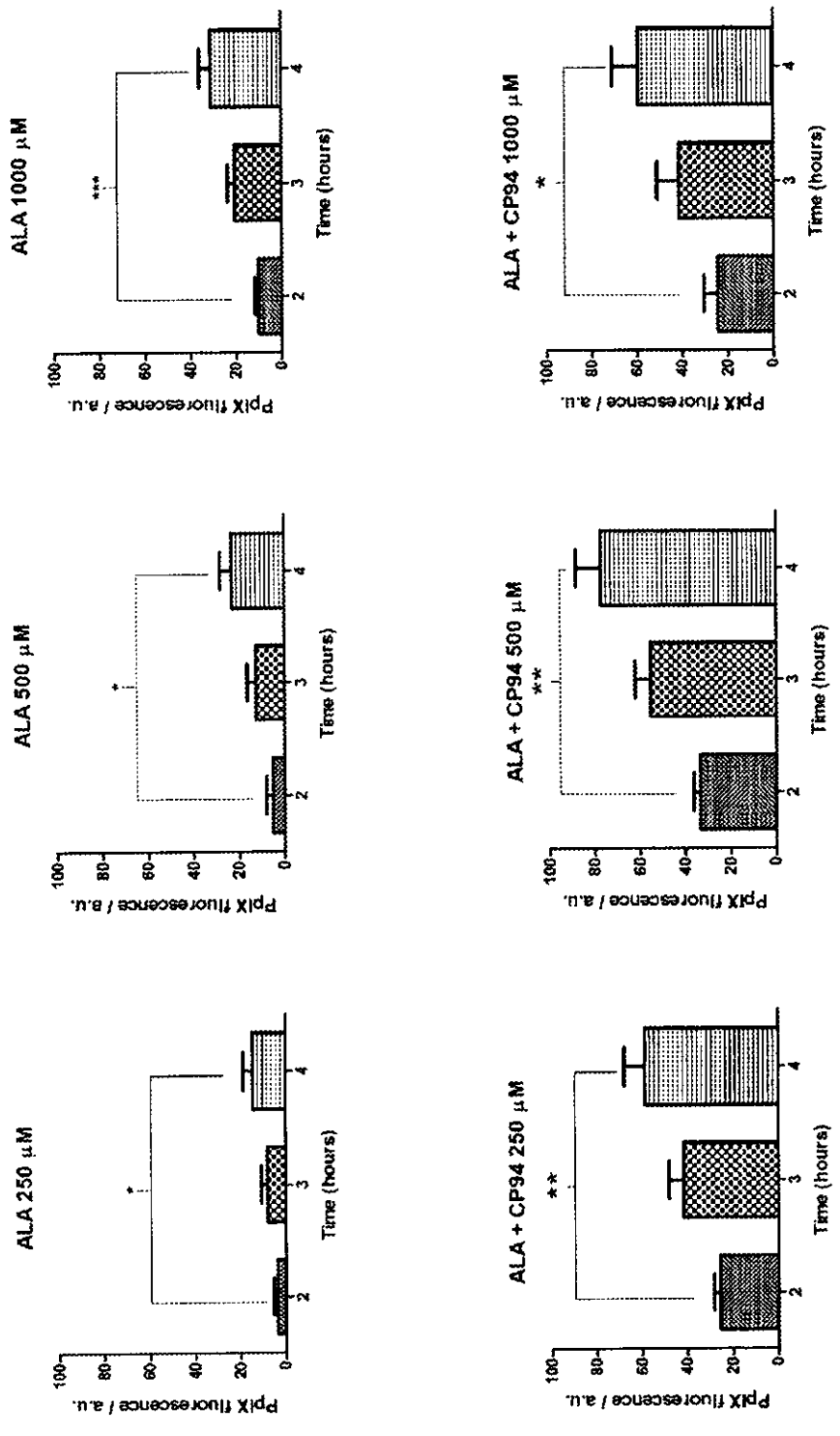

Figure 8A

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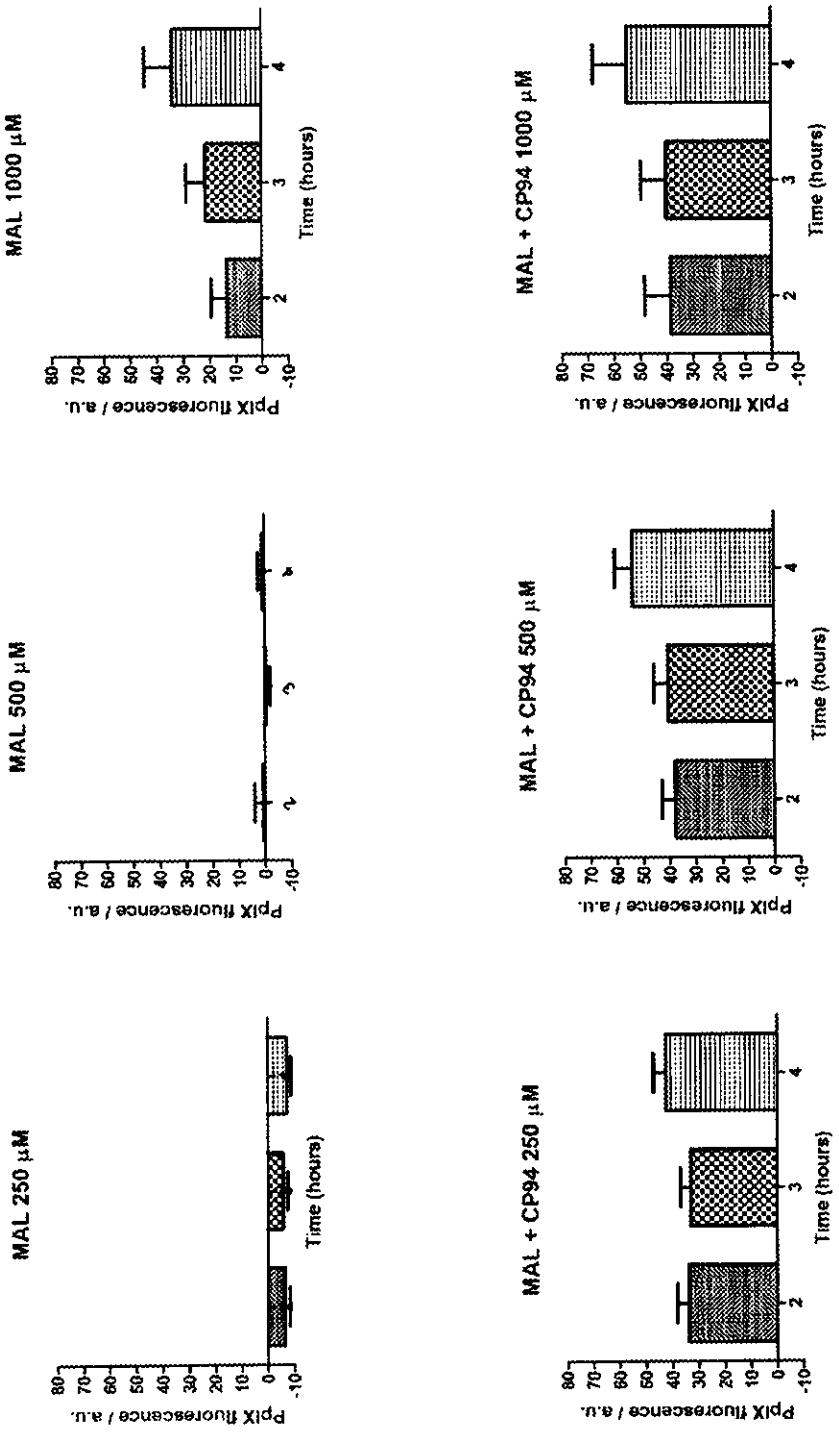

Figure 8B

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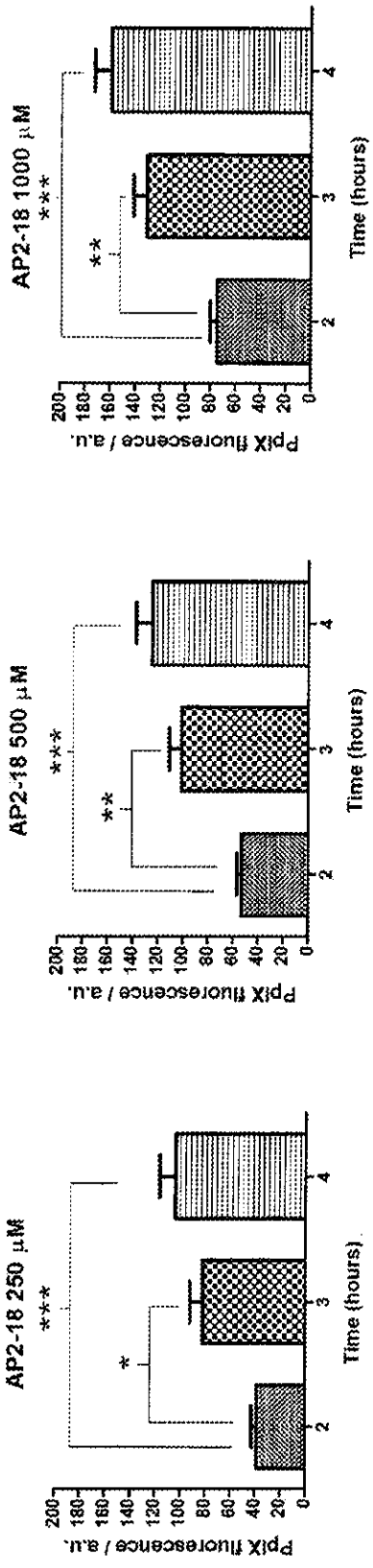

Figure 8C

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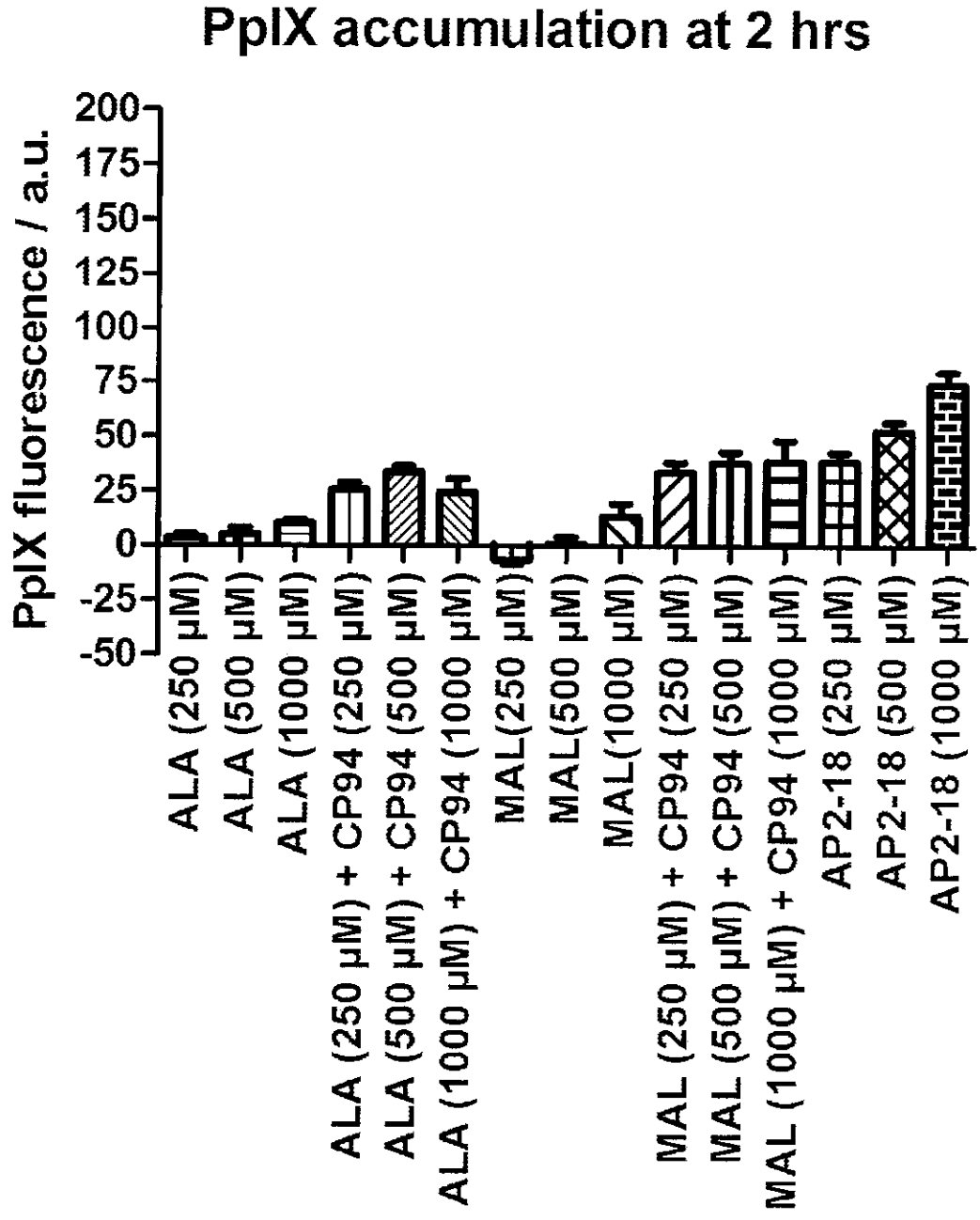
PpIX accumulation at 2 hrs
PpIX fluorescence / a.u.
200
175
150
125
100
75
50
25
0
-25
-50
ALA (250 µM)
ALA (500 µM)
ALA (1000 µM)
ALA (250 µM) + CP94 (250 µM)
ALA (500 µM) + CP94 (500 µM)
ALA (1000 µM) + CP94 (1000 µM)
MAL(250 µM)
MAL(500 µM)
MAL(1000 µM)
MAL (250 µM) + CP94 (250 µM)
MAL (500 µM) + CP94 (500 µM)
MAL (1000 µM) + CP94 (1000 µM)
AP2-18 (250 µM)
AP2-18 (500 µM)
AP2-18 (1000 µM)

Figure 9A(i)

AP2-18 (250 µM)

vs	
ALA (250 µM)	P<0.05
ALA (500 µM)	n.s
ALA (1000 µM)	n.s
ALA (250 µM) + CP94 (250 µM)	n.s
ALA (500 µM) + CP94 (500 µM)	n.s
ALA (1000 µM) + CP94 (1000 µM)	n.s
MAL (250 µM)	P<0.001
MAL (500 µM)	P<0.001
MAL (1000 µM)	n.s
MAL (250 µM) + CP94 (250 µM)	n.s
MAL (500 µM) + CP94 (500 µM)	n.s
MAL (1000 µM) + CP94 (1000 µM)	n.s
AP-18 (250 µM)	
AP-18 (500 µM)	n.s
AP-18 (1000 µM)	P<0.01

AP2-18 (500 µM)

vs	
ALA (250 µM)	P<0.001
ALA (500 µM)	P<0.001
ALA (1000 µM)	P<0.01
ALA (250 µM) + CP94 (250 µM)	n.s
ALA (500 µM) + CP94 (500 µM)	n.s
ALA (1000 µM) + CP94 (1000 µM)	n.s
MAL (250 µM)	P<0.001
MAL (500 µM)	P<0.001
MAL (1000 µM)	P<0.05
MAL (250 µM) + CP94 (250 µM)	P<0.05
MAL (500 µM) + CP94 (500 µM)	n.s
MAL (1000 µM) + CP94 (1000 µM)	n.s
AP-18 (250 µM)	n.s
AP-18 (500 µM)	
AP-18 (1000 µM)	n.s

AP2-18 (1000 µM)

vs	
ALA (250 µM)	P<0.001
ALA (500 µM)	P<0.001
ALA (1000 µM)	P<0.001
ALA (250 µM) + CP94 (250 µM)	P<0.001
ALA (500 µM) + CP94 (500 µM)	P<0.05
ALA (1000 µM) + CP94 (1000 µM)	P<0.001
MAL (250 µM)	P<0.001
MAL (500 µM)	P<0.001
MAL (1000 µM)	P<0.001
MAL (250 µM) + CP94 (250 µM)	P<0.001
MAL (500 µM) + CP94 (500 µM)	P<0.001
MAL (1000 µM) + CP94 (1000 µM)	P<0.01
AP-18 (250 µM)	P<0.01
AP-18 (500 µM)	n.s
AP-18 (1000 µM)	

P<....	Significantly greater than
P<...	Significantly less than
n.s	No significant difference

Figure 9A(ii)

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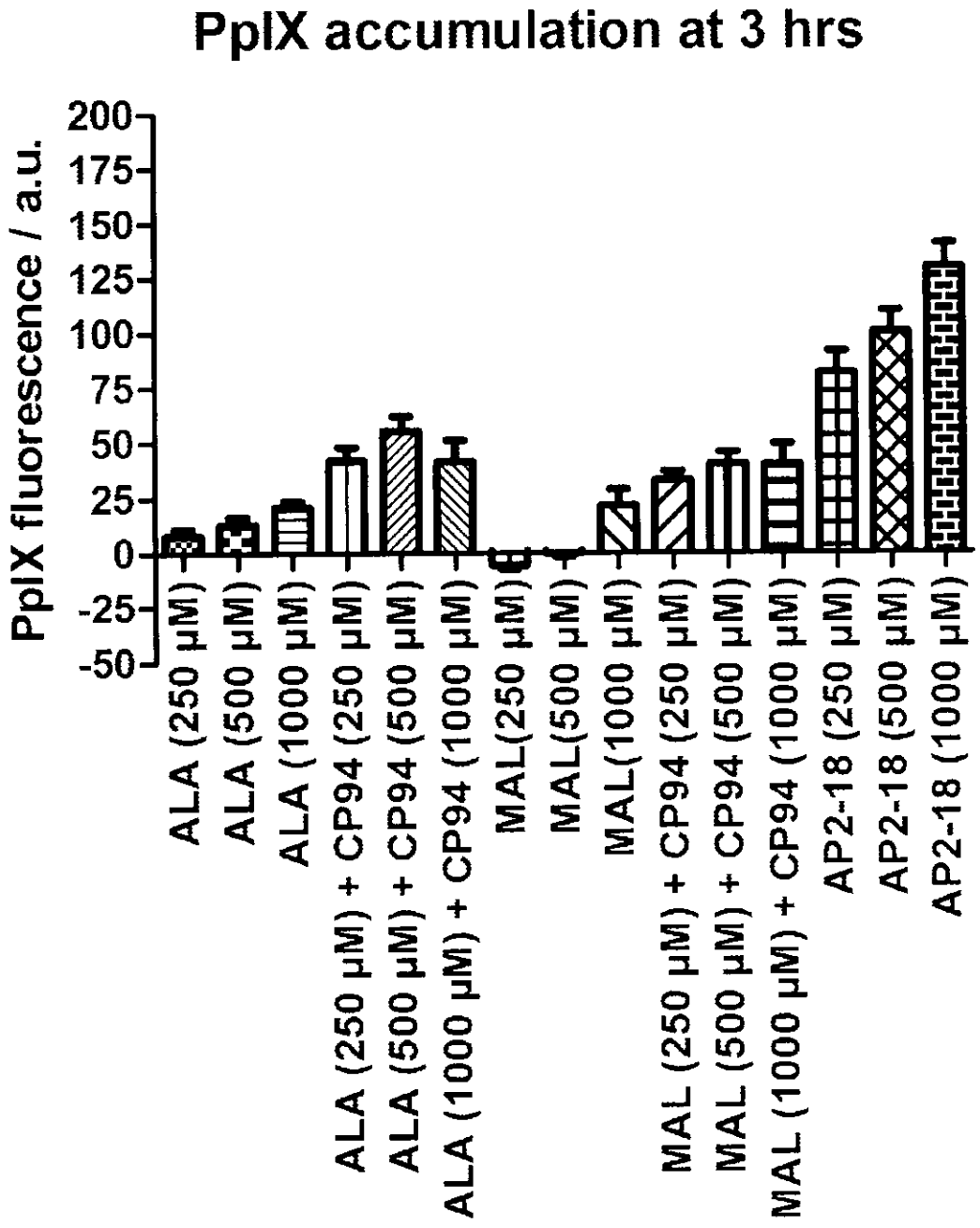

Figure 9B(i)

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AP2-18 (250 µM)

vs	
ALA (250 µM)	P<0.001
ALA (500 µM)	P<0.01
ALA (1000 µM)	P<0.05
ALA (250 µM) + CP94 (250 µM)	n.s
ALA (500 µM) + CP94 (500 µM)	n.s
ALA (1000 µM) + CP94 (1000 µM)	n.s
MAL (250 µM)	P<0.001
MAL (500 µM)	P<0.001
MAL (1000 µM)	n.s
MAL (250 µM) + CP94 (250 µM)	n.s
MAL (500 µM) + CP94 (500 µM)	n.s
MAL (1000 µM) + CP94 (1000 µM)	n.s
AP-18 (250 µM)	
AP-18 (500 µM)	n.s
AP-18 (1000 µM)	P<0.001

AP2-18 (500 µM)

vs	
ALA (250 µM)	P<0.001
ALA (500 µM)	P<0.001
ALA (1000 µM)	P<0.001
ALA (250 µM) + CP94 (250 µM)	n.s
ALA (500 µM) + CP94 (500 µM)	n.s
ALA (1000 µM) + CP94 (1000 µM)	n.s
MAL (250 µM)	P<0.001
MAL (500 µM)	P<0.001
MAL (1000 µM)	P<0.01
MAL (250 µM) + CP94 (250 µM)	P<0.001
MAL (500 µM) + CP94 (500 µM)	P<0.01
MAL (1000 µM) + CP94 (1000 µM)	n.s
AP-18 (250 µM)	n.s
AP-18 (500 µM)	
AP-18 (1000 µM)	n.s

AP2-18 (1000 µM)

vs	
ALA (250 µM)	P<0.001
ALA (500 µM)	P<0.001
ALA (1000 µM)	P<0.001
ALA (250 µM) + CP94 (250 µM)	P<0.001
ALA (500 µM) + CP94 (500 µM)	n.s
ALA (1000 µM) + CP94 (1000 µM)	P<0.001
MAL (250 µM)	P<0.001
MAL (500 µM)	P<0.001
MAL (1000 µM)	P<0.001
MAL (250 µM) + CP94 (250 µM)	P<0.001
MAL (500 µM) + CP94 (500 µM)	P<0.001
MAL (1000 µM) + CP94 (1000 µM)	P<0.01
AP-18 (250 µM)	P<0.001
AP-18 (500 µM)	n.s
AP-18 (1000 µM)	

P<....	Significantly greater than
P<....	Significantly less than
n.s	No significant difference

Figure 9B(ii)

(H. SUBRAMANIAM)
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Attorneys for the applicants

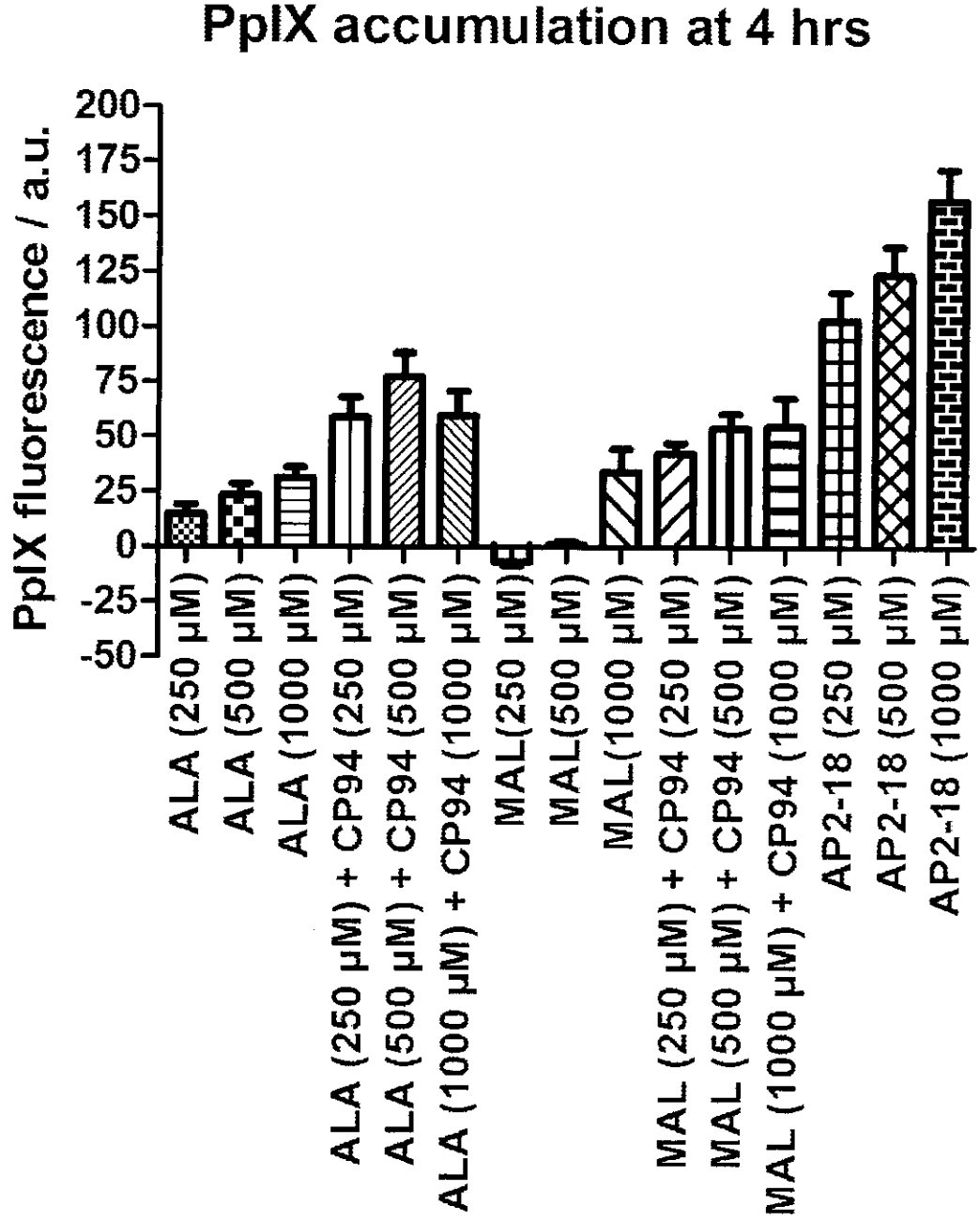

Figure 9C(i)

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AP2-18 (250 µM)	
vs	
ALA (250 µM)	P<0.001
ALA (500 µM)	P<0.001
ALA (1000 µM)	P<0.01
ALA (250 µM) + CP94 (250 µM)	n.s
ALA (500 µM) + CP94 (500 µM)	n.s
ALA (1000 µM) + CP94 (1000 µM)	n.s
MAL (250 µM)	P<0.001
MAL (500 µM)	P<0.001
MAL (1000 µM)	n.s
MAL (250 µM) + CP94 (250 µM)	P<0.001
MAL (500 µM) + CP94 (500 µM)	P<0.05
MAL (1000 µM) + CP94 (1000 µM)	n.s
AP-18 (250 µM)	
AP-18 (500 µM)	n.s
AP-18 (1000 µM)	P<0.001
AP2-18 (500 µM)	
vs	
ALA (250 µM)	P<0.001
ALA (500 µM)	P<0.001
ALA (1000 µM)	P<0.001
ALA (250 µM) + CP94 (250 µM)	n.s
ALA (500 µM) + CP94 (500 µM)	n.s
ALA (1000 µM) + CP94 (1000 µM)	n.s
MAL (250 µM)	P<0.001
MAL (500 µM)	P<0.001
MAL (1000 µM)	P<0.001
MAL (250 µM) + CP94 (250 µM)	P<0.001
MAL (500 µM) + CP94 (500 µM)	P<0.001
MAL (1000 µM) + CP94 (1000 µM)	n.s
AP-18 (250 µM)	n.s
AP-18 (500 µM)	
AP-18 (1000 µM)	P<0.05
AP2-18 (1000 µM)	
vs	
ALA (250 µM)	P<0.001
ALA (500 µM)	P<0.001
ALA (1000 µM)	P<0.001
ALA (250 µM) + CP94 (250 µM)	P<0.001
ALA (500 µM) + CP94 (500 µM)	P<0.05
ALA (1000 µM) + CP94 (1000 µM)	P<0.001
MAL (250 µM)	P<0.001
MAL (500 µM)	P<0.001
MAL (1000 µM)	P<0.001
MAL (250 µM) + CP94 (250 µM)	P<0.001
MAL (500 µM) + CP94 (500 µM)	P<0.001
MAL (1000 µM) + CP94 (1000 µM)	P<0.001
AP-18 (250 µM)	P<0.001
AP-18 (500 µM)	P<0.05
AP-18 (1000 µM)	

P<....	Significantly greater than
P<....	Significantly less than
n.s	No significant difference

Figure 9C(ii)

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Attorneys for the applicants

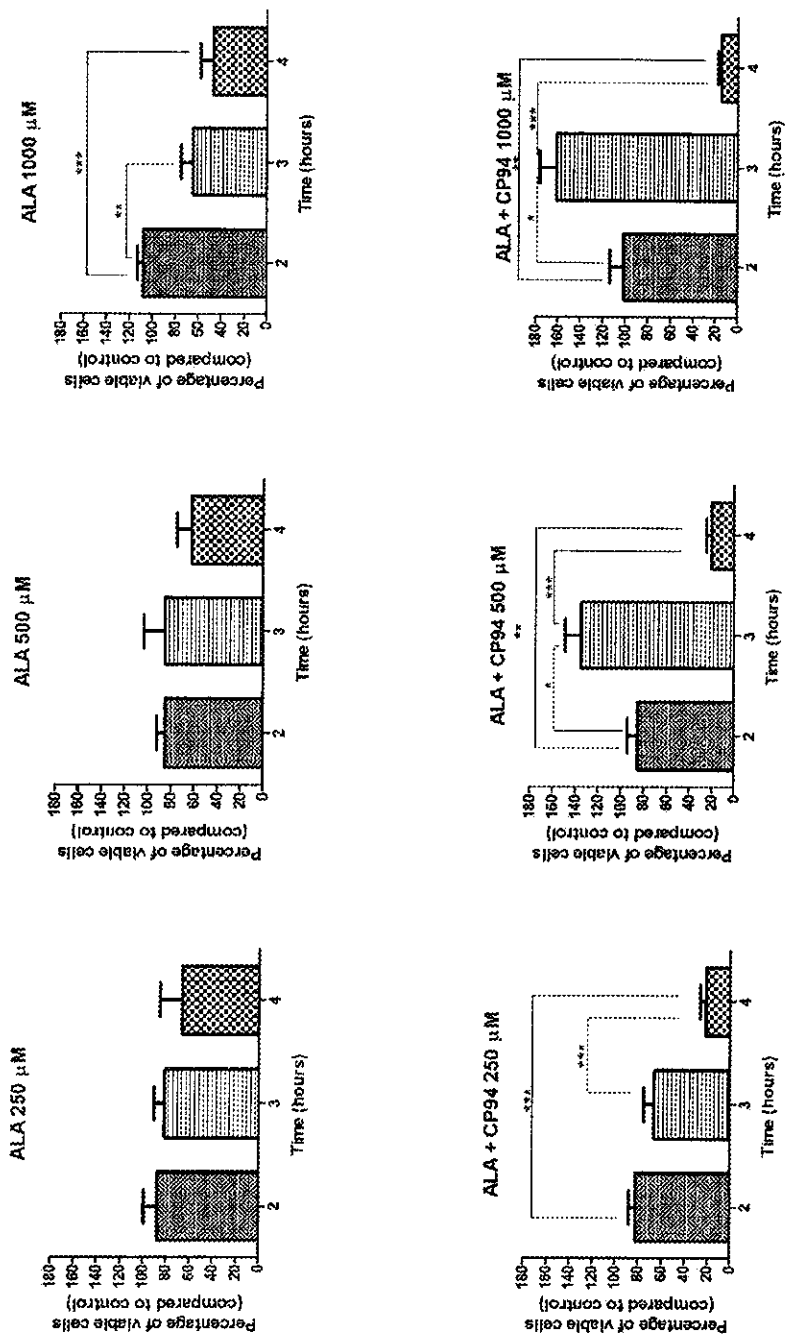

Figure 10A

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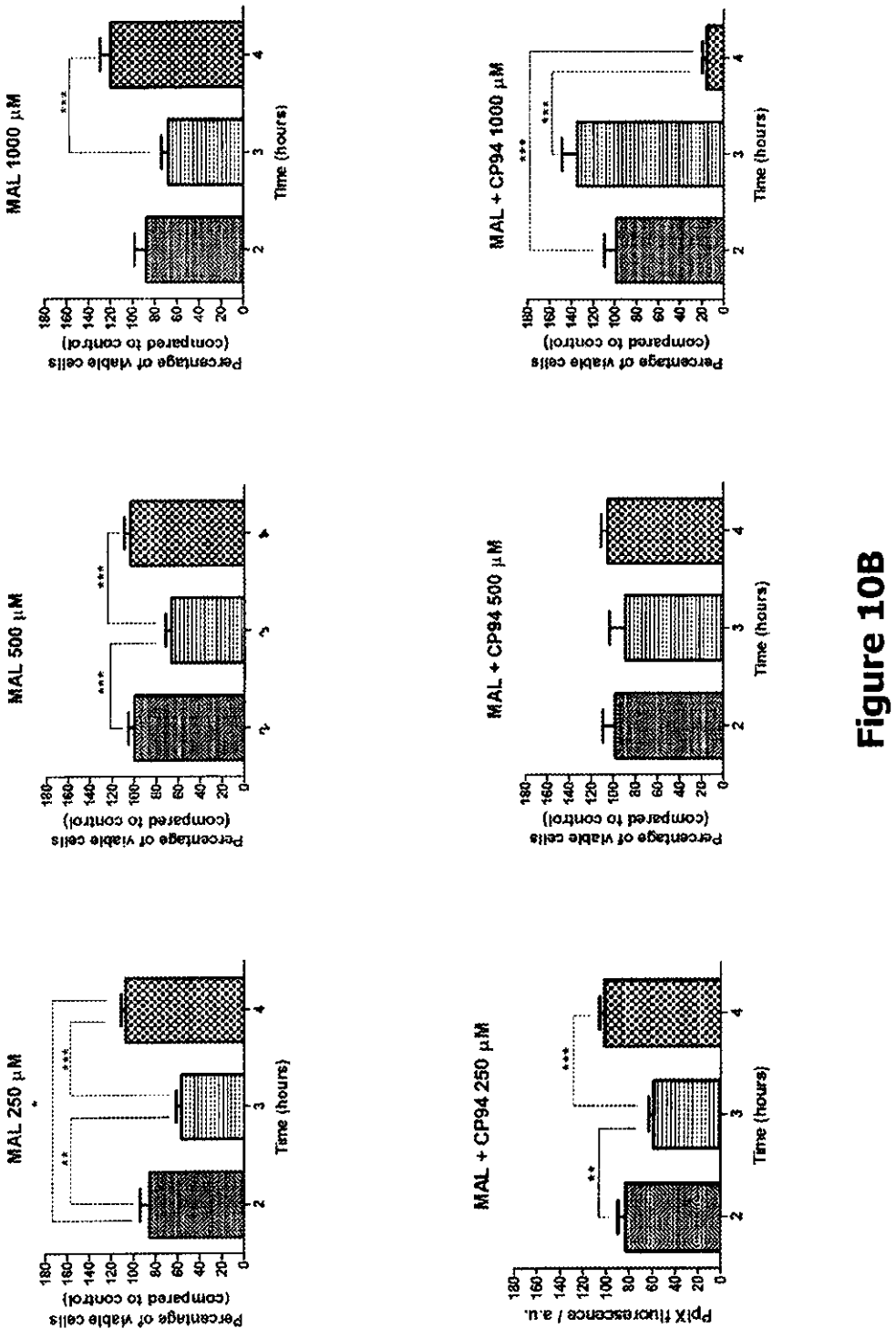

Figure 10B

(H. SUBRAMANIAM)
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Attorneys for the applicants

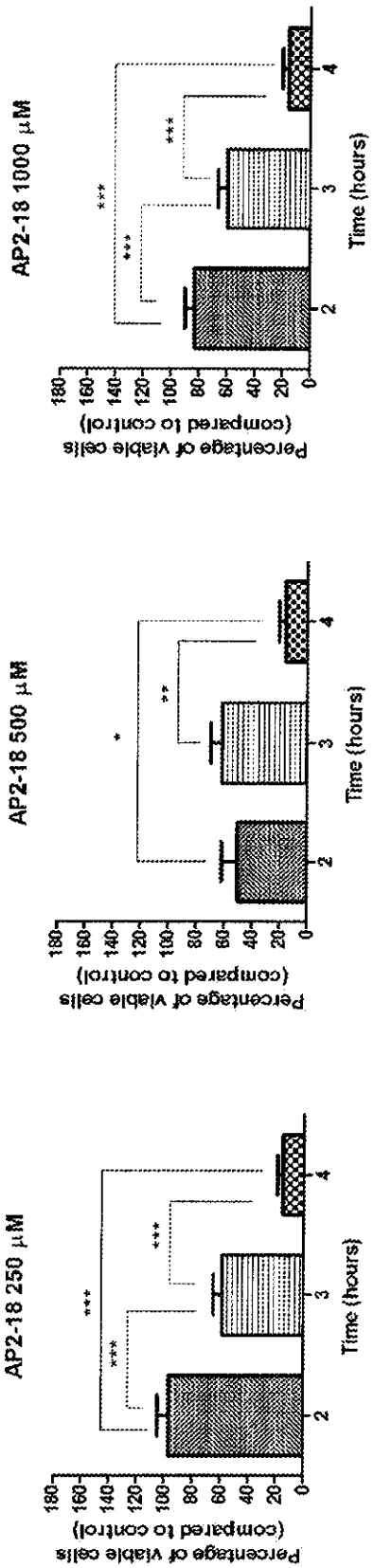

Figure 10C

(H. SUBRAMANIAM)
of SUBRAMANIAM & ASSOCIATES
Attorneys for the applicants

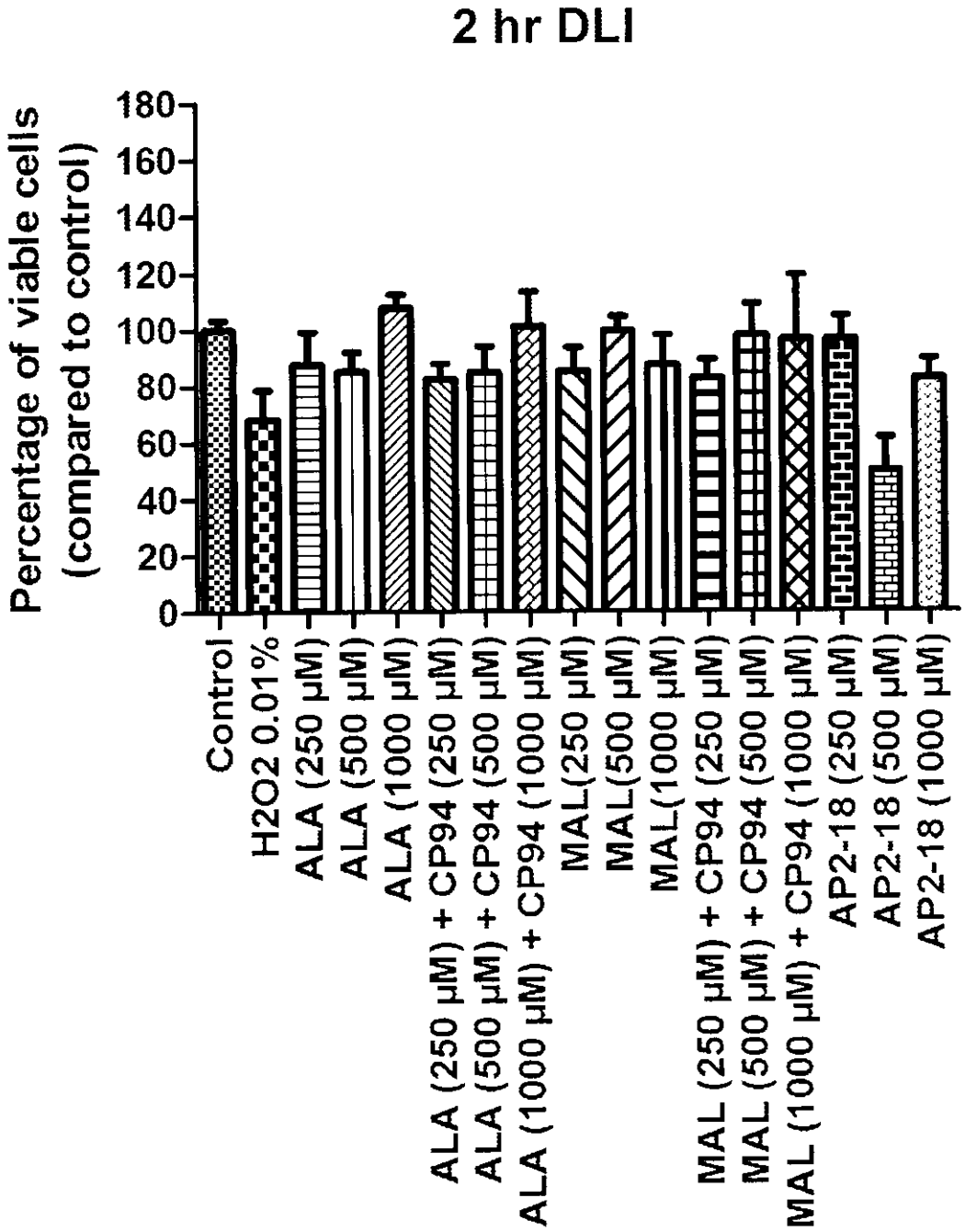
2 hr DLI
Percentage of viable cells (compared to control)
180
160
140
120
100
80
60
40
20
0
Control
H2O2 0.01%
ALA (250 µM)
ALA (500 µM)
ALA (1000 µM)
ALA (250 µM) + CP94 (250 µM)
ALA (500 µM) + CP94 (500 µM)
ALA (1000 µM) + CP94 (1000 µM)
MAL(250 µM)
MAL(500 µM)
MAL(1000 µM)
MAL (250 µM) + CP94 (250 µM)
MAL (500 µM) + CP94 (500 µM)
MAL (1000 µM) + CP94 (1000 µM)
AP2-18 (250 µM)
AP2-18 (500 µM)
AP2-18 (1000 µM)

Figure 11A(i)

AP2-18 (250 µM)	
vs	
Untreated	n.s
ALA (250 µM)	n.s
ALA (500 µM)	n.s
ALA (1000 µM)	n.s
ALA (250 µM) + CP94 (250 µM)	n.s
ALA (500 µM) + CP94 (500 µM)	n.s
ALA (1000 µM) + CP94 (1000 µM)	n.s
MAL (250 µM)	n.s
MAL (500 µM)	n.s
MAL (1000 µM)	n.s
MAL (250 µM) + CP94 (250 µM)	n.s
MAL (500 µM) + CP94 (500 µM)	n.s
MAL (1000 µM) + CP94 (1000 µM)	n.s
AP-18 (250 µM)	
AP-18 (500 µM)	n.s
AP-18 (1000 µM)	n.s
AP2-18 (500 µM)	
vs	
Untreated	n.s
ALA (250 µM)	n.s
ALA (500 µM)	n.s
ALA (1000 µM)	P<0.05
ALA (250 µM) + CP94 (250 µM)	n.s
ALA (500 µM) + CP94 (500 µM)	n.s
ALA (1000 µM) + CP94 (1000 µM)	n.s
MAL (250 µM)	n.s
MAL (500 µM)	n.s
MAL (1000 µM)	n.s
MAL (250 µM) + CP94 (250 µM)	n.s
MAL (500 µM) + CP94 (500 µM)	n.s
MAL (1000 µM) + CP94 (1000 µM)	n.s
AP-18 (250 µM)	n.s
AP-18 (500 µM)	
AP-18 (1000 µM)	n.s
AP2-18 (1000 µM) vs	
Untreated	n.s
ALA (250 µM)	n.s
ALA (500 µM)	n.s
ALA (1000 µM)	n.s
ALA (250 µM) + CP94 (250 µM)	n.s
ALA (500 µM) + CP94 (500 µM)	n.s
ALA (1000 µM) + CP94 (1000 µM)	n.s
MAL (250 µM)	n.s
MAL (500 µM)	n.s
MAL (1000 µM)	n.s
MAL (250 µM) + CP94 (250 µM)	n.s
MAL (500 µM) + CP94 (500 µM)	n.s
MAL (1000 µM) + CP94 (1000 µM)	n.s
AP-18 (250 µM)	n.s
AP-18 (500 µM)	n.s
AP-18 (1000 µM)	

P<....	Significantly greater than
P<....	Significantly less than
n.s	No significant difference

Figure 11A(ii)

(H. SUBRAMANIAM)
of SUBRAMANIAM & ASSOCIATES
Attorneys for the applicants

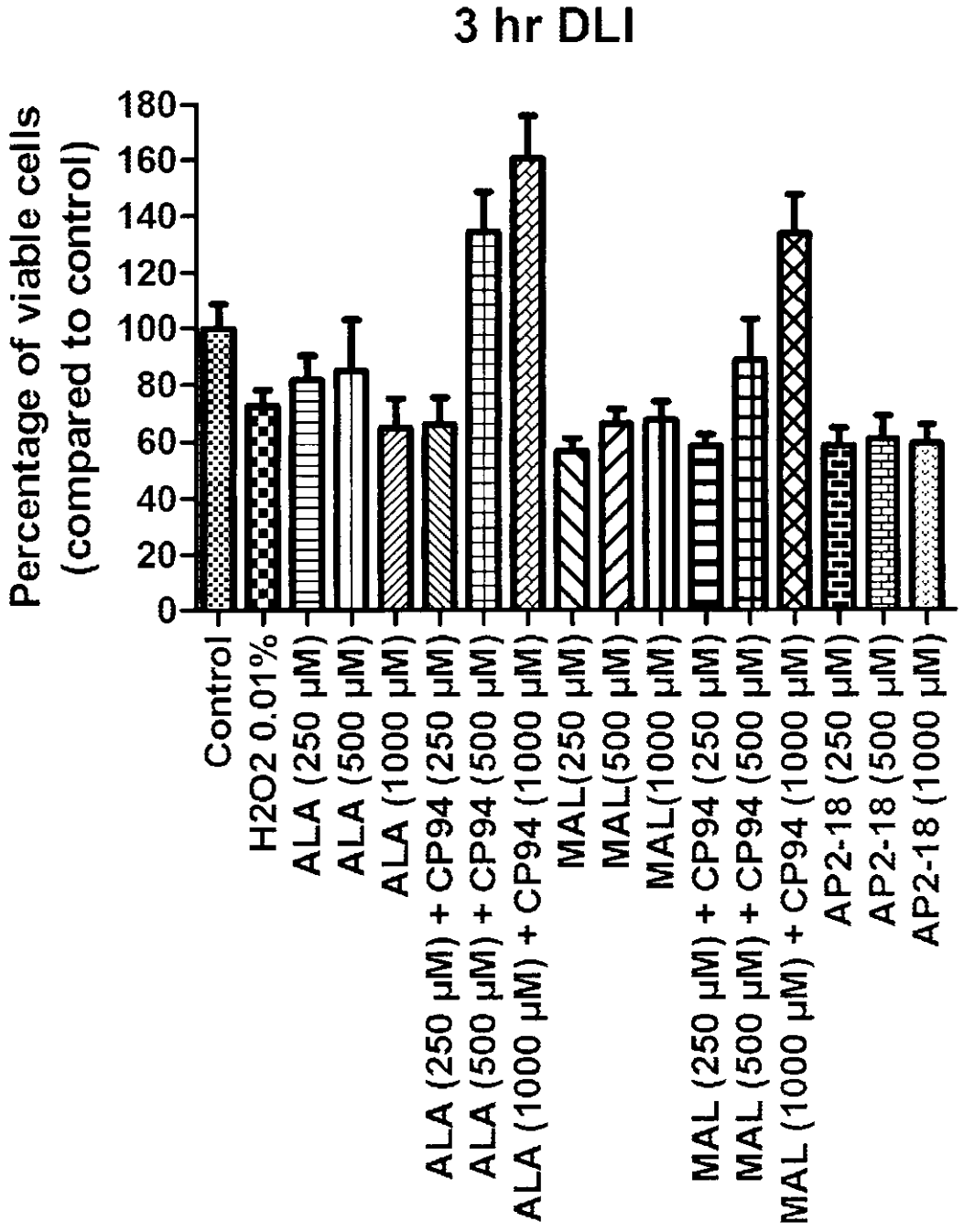
3 hr DLI
Percentage of viable cells (compared to control)
180
160
140
120
100
80
60
40
20
0
Control
H2O2 0.01%
ALA (250 µM)
ALA (500 µM)
ALA (1000 µM)
ALA (250 µM) + CP94 (250 µM)
ALA (500 µM) + CP94 (500 µM)
ALA (1000 µM) + CP94 (1000 µM)
MAL(250 µM)
MAL(500 µM)
MAL(1000 µM)
MAL (250 µM) + CP94 (250 µM)
MAL (500 µM) + CP94 (500 µM)
MAL (1000 µM) + CP94 (1000 µM)
AP2-18 (250 µM)
AP2-18 (500 µM)
AP2-18 (1000 µM)

Figure 11B(i)

AP2-18 (250 µM) vs	
Untreated	n.s
ALA (250 µM)	n.s
ALA (500 µM)	n.s
ALA (1000 µM)	n.s
ALA (250 µM) + CP94 (250 µM)	n.s
ALA (500 µM) + CP94 (500 µM)	P<0.001
ALA (1000 µM) + CP94 (1000 µM)	P<0.001
MAL (250 µM)	n.s
MAL (500 µM)	n.s
MAL (1000 µM)	n.s
MAL (250 µM) + CP94 (250 µM)	n.s
MAL (500 µM) + CP94 (500 µM)	n.s
MAL (1000 µM) + CP94 (1000 µM)	P<0.001
AP-18 (250 µM)	
AP-18 (500 µM)	n.s
AP-18 (1000 µM)	n.s
AP2-18 (500 µM) vs	
Untreated	n.s
ALA (250 µM)	n.s
ALA (500 µM)	n.s
ALA (1000 µM)	P<0.05
ALA (250 µM) + CP94 (250 µM)	n.s
ALA (500 µM) + CP94 (500 µM)	P<0.001
ALA (1000 µM) + CP94 (1000 µM)	P<0.001
MAL (250 µM)	n.s
MAL (500 µM)	n.s
MAL (1000 µM)	n.s
MAL (250 µM) + CP94 (250 µM)	n.s
MAL (500 µM) + CP94 (500 µM)	n.s
MAL (1000 µM) + CP94 (1000 µM)	P<0.001
AP-18 (250 µM)	n.s
AP-18 (500 µM)	
AP-18 (1000 µM)	n.s
AP2-18 (1000 µM) vs	
Untreated	n.s
ALA (250 µM)	n.s
ALA (500 µM)	n.s
ALA (1000 µM)	n.s
ALA (250 µM) + CP94 (250 µM)	n.s
ALA (500 µM) + CP94 (500 µM)	P<0.001
ALA (1000 µM) + CP94 (1000 µM)	P<0.001
MAL (250 µM)	n.s
MAL (500 µM)	n.s
MAL (1000 µM)	n.s
MAL (250 µM) + CP94 (250 µM)	n.s
MAL (500 µM) + CP94 (500 µM)	n.s
MAL (1000 µM) + CP94 (1000 µM)	P<0.001
AP-18 (250 µM)	n.s
AP-18 (500 µM)	n.s
AP-18 (1000 µM)	

P<....	Significantly greater than
P<...	Significantly less than
n.s	No significant difference

Figure 11B(ii)

(H. SUBRAMANIAM)
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Attorneys for the applicants

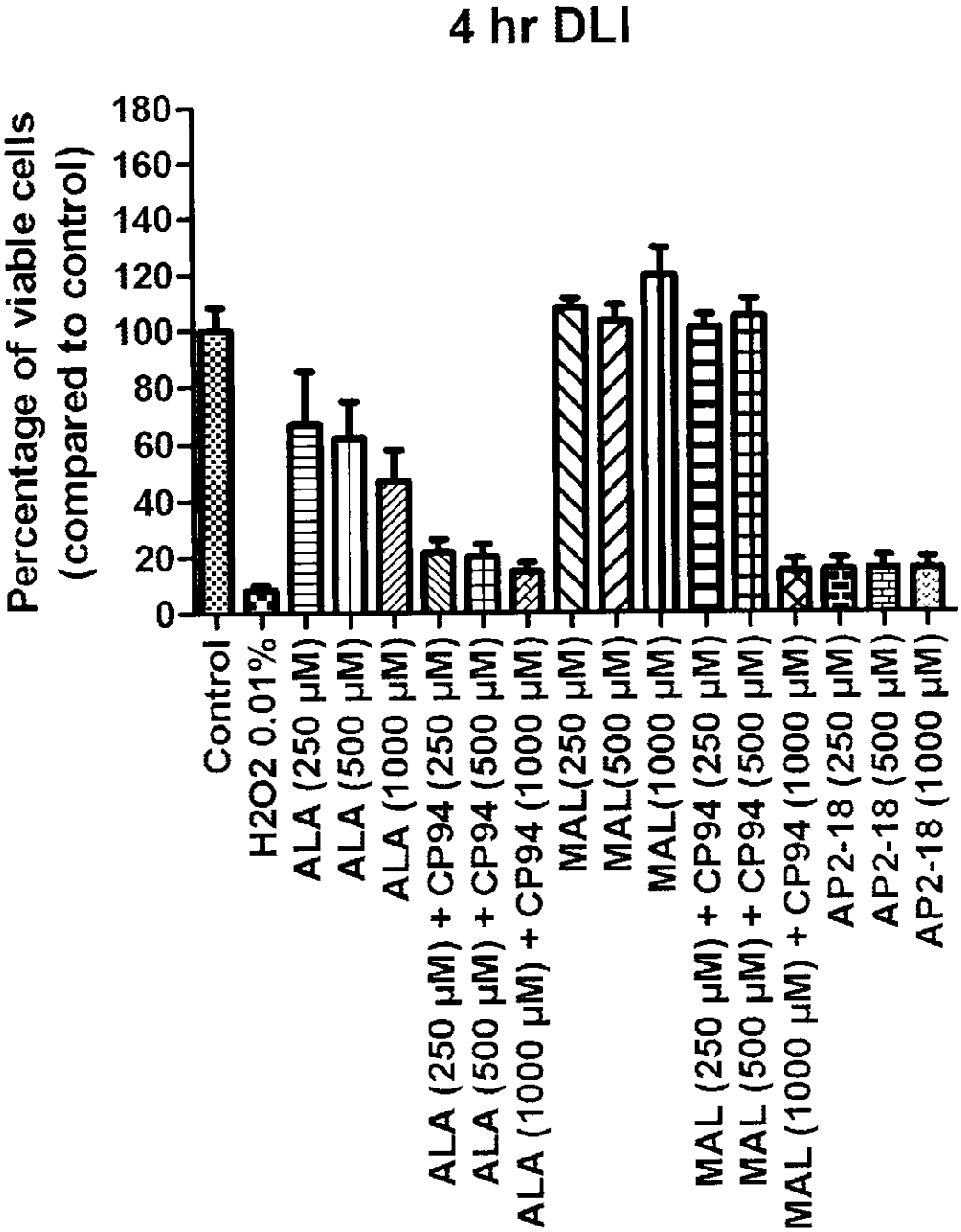
4 hr DLI
Percentage of viable cells (compared to control)
180
160
140
120
100
80
60
40
20
0
Control
H2O2 0.01%
ALA (250 µM)
ALA (500 µM)
ALA (1000 µM)
ALA (250 µM) + CP94 (250 µM)
ALA (500 µM) + CP94 (500 µM)
ALA (1000 µM) + CP94 (1000 µM)
MAL(250 µM)
MAL(500 µM)
MAL(1000 µM)
MAL (250 µM) + CP94 (250 µM)
MAL (500 µM) + CP94 (500 µM)
MAL (1000 µM) + CP94 (1000 µM)
AP2-18 (250 µM)
AP2-18 (500 µM)
AP2-18 (1000 µM)

Figure 11C(i)

AP2-18 (250 µM) vs	
Untreated	P<0.001
ALA (250 µM)	P<0.01
ALA (500 µM)	P<0.05
ALA (1000 µM)	n.s
ALA (250 µM) + CP94 (250 µM)	n.s
ALA (500 µM) + CP94 (500 µM)	n.s
ALA (1000 µM) + CP94 (1000 µM)	n.s
MAL (250 µM)	P<0.001
MAL (500 µM)	P<0.001
MAL (1000 µM)	P<0.001
MAL (250 µM) + CP94 (250 µM)	P<0.001
MAL (500 µM) + CP94 (500 µM)	P<0.001
MAL (1000 µM) + CP94 (1000 µM)	n.s
AP-18 (250 µM)	
AP-18 (500 µM)	n.s
AP-18 (1000 µM)	n.s
AP2-18 (500 µM) vs	
Untreated	P<0.001
ALA (250 µM)	P<0.01
ALA (500 µM)	P<0.05
ALA (1000 µM)	n.s
ALA (250 µM) + CP94 (250 µM)	n.s
ALA (500 µM) + CP94 (500 µM)	n.s
ALA (1000 µM) + CP94 (1000 µM)	n.s
MAL (250 µM)	P<0.001
MAL (500 µM)	P<0.001
MAL (1000 µM)	P<0.001
MAL (250 µM) + CP94 (250 µM)	P<0.001
MAL (500 µM) + CP94 (500 µM)	P<0.001
MAL (1000 µM) + CP94 (1000 µM)	n.s
AP-18 (250 µM)	n.s
AP-18 (500 µM)	
AP-18 (1000 µM)	n.s
AP2-18 (1000 µM) vs	
Untreated	P<0.001
ALA (250 µM)	P<0.01
ALA (500 µM)	P<0.05
ALA (1000 µM)	n.s
ALA (250 µM) + CP94 (250 µM)	n.s
ALA (500 µM) + CP94 (500 µM)	n.s
ALA (1000 µM) + CP94 (1000 µM)	n.s
MAL (250 µM)	P<0.001
MAL (500 µM)	P<0.001
MAL (1000 µM)	P<0.001
MAL (250 µM) + CP94 (250 µM)	P<0.001
MAL (500 µM) + CP94 (500 µM)	P<0.001
MAL (1000 µM) + CP94 (1000 µM)	n.s
AP-18 (250 µM)	n.s
AP-18 (500 µM)	n.s
AP-18 (1000 µM)	

P<....	Significantly greater than
P<....	Significantly less than
n.s	No significant difference

Figure 11C(ii)

(H. SUBRAMANIAM)
of SUBRAMANIAM & ASSOCIATES
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