The 8th International Electronic Conference on Medicinal Chemistry (ECMC 2022)
01–30 NOVEMBER 2022 | ONLINE

Evaluation of cytotoxic activity of small aminated quinolinequinones *in vitro* as anti cancer molecules

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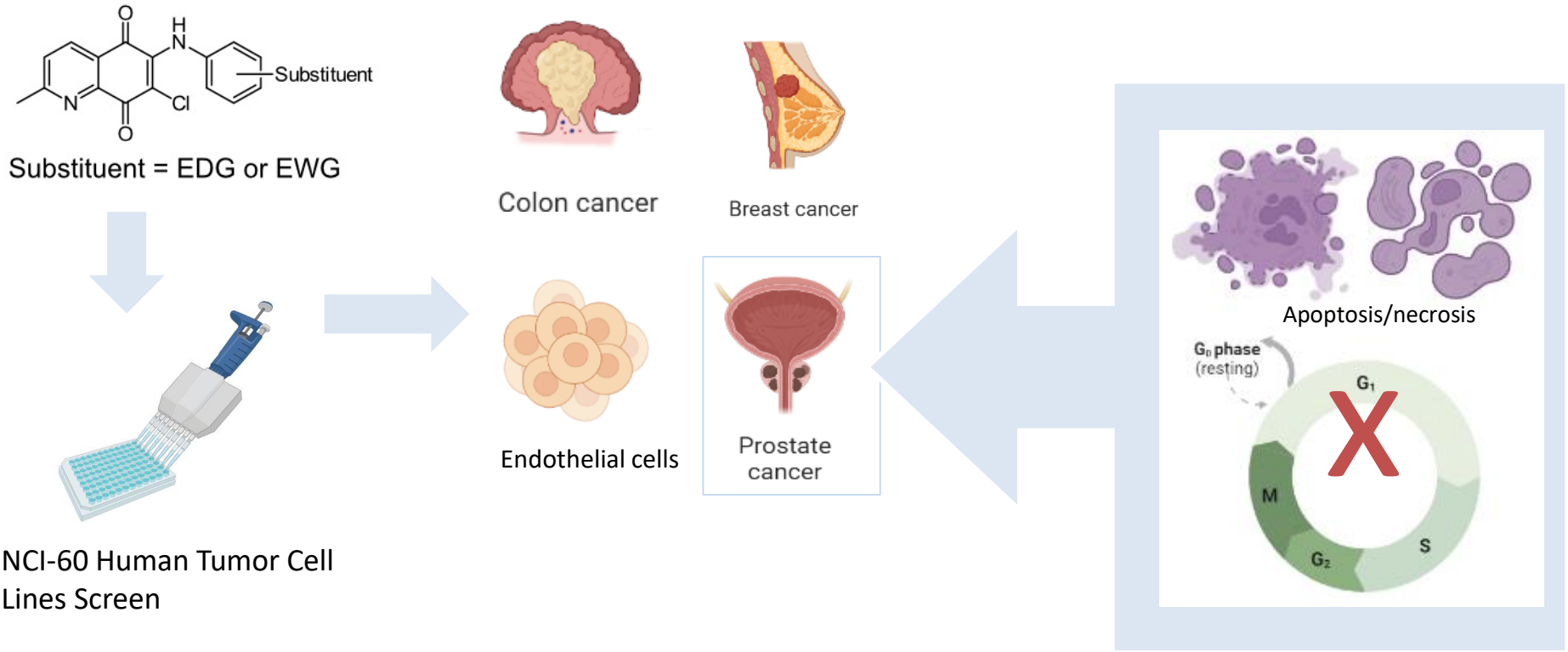
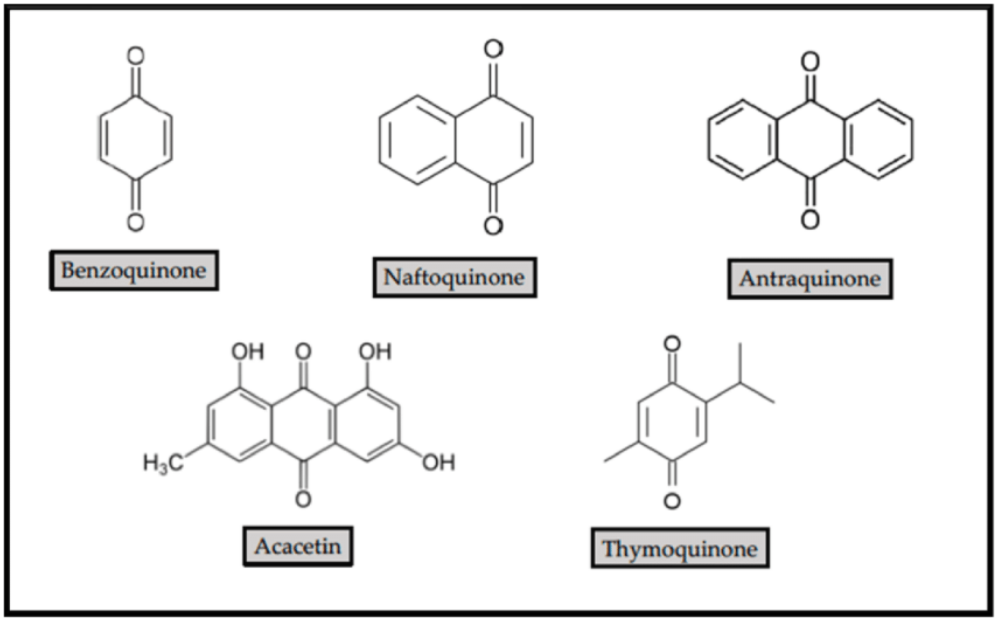
Evaluation of cytotoxic activity of small aminated quinolinequinones *in vitro* as anti cancer molecules

Graphical Abstract



Introduction

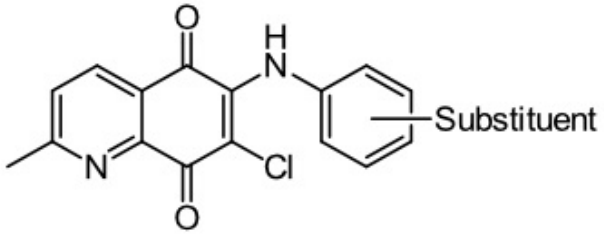
- Quinones are one of the most significant and widely dispersed chemical family.
- Widely found in natural products.
- Quinone derivates have been reported to have a range of biological traits such as antibacterial, anticancer, antifungal and anti-inflammatory activities.



DOI:
10.1002/slct.201700692
10.1021/jm301689x
10.1007/BF02975419
10.1007/BF02975419
10.1016/j.bmc.2008.09.052

Introduction

- As quinone derivates our group recently reported the synthesis of two subseries of aminated quinolinequinones (AQQs, AQQ1–16) and their antibacterial activity.



Substituent = EDG or EWG

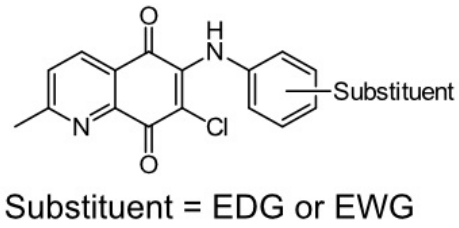
ID	EWG	ID	EDG	ID	EDG
AQQ1	2-CF_3	**AQQ6**	3-CH_3	**AQQ12**	2,3-diCH_3
AQQ2	3-CF_3	**AQQ7**	4-CH_3	**AQQ13**	2,4-diCH_3
AQQ3	4-CF_3	**AQQ8**	2-$CH(CH_3)_2$	**AQQ14**	2,5-diCH_3
AQQ4	4-CN	**AQQ9**	3-$CH(CH_3)_2$	**AQQ15**	3,4-diCH_3
AQQ5	3,5-diCF_3	**AQQ10**	4-$CH(CH_3)_2$	**AQQ16**	3,5-diCH_3
		AQQ11	4-$N(CH_2CH_3)_2$		

DOI:10.1016/j.bioorg.2022.106045

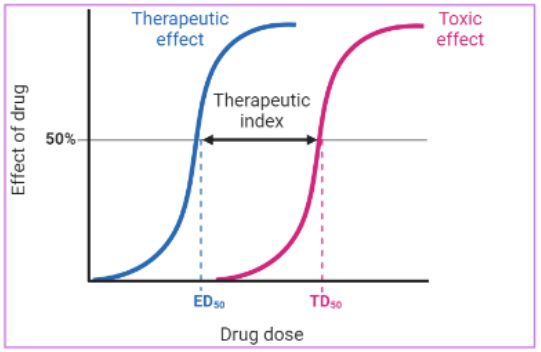
Introduction

- Thus, compounds were sent to NCI Developmental Therapeutics Program

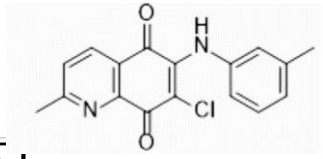
NCI-60 Human Tumor Cell Lines Screen

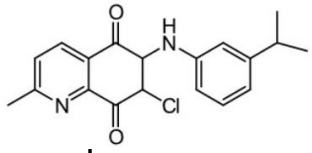


Substituent = EDG or EWG



- The findings indicated good cytotoxicity against some cancer types.





Developmental Therapeutics Program

One Dose Mean Graph

AQQ6

Panel/Cell Line	Growth Percent
Leukemia	
CCRF-CEM	3.19
HL-60(TB)	-14.92
K-562	2.91
MOLT-4	-22.12
SR	1.13
Non-Small Cell Lung Cancer	
A549/ATCC	16.68
EKVX	75.74
HOP-62	42.75
HOP-92	-68.71
NCI-H226	-0.04
NCI-H23	-27.79
NCI-H322M	13.51
NCI-H460	5.47
NCI-H522	-24.02
Colon Cancer	
COLO 205	111.43
HCC-2998	3.47
HCT-116	-47.65
HCT-15	-54.84
HT29	114.86
KM12	33.48
SW-620	-13.67
CNS Cancer	
SF-268	58.19
SF-295	12.67
SF-539	-78.99
SNB-19	23.72
SNB-75	-64.89
U251	32.77
Melanoma	
LOX IMVI	-54.55
MALME-3M	-75.34
M14	-45.02
SK-MEL-2	-9.34
SK-MEL-28	-54.46
SK-MEL-5	-92.98
UACC-257	-80.23
UACC-62	-67.02
Ovarian Cancer	
IGROV1	-54.14
OVCAR-3	-31.84
OVCAR-4	-97.54
OVCAR-5	-43.02
OVCAR-8	6.03
NCI/ADR-RES	13.77
SK-OV-3	74.46
Renal Cancer	
786-0	3.53
A498	42.15
ACHN	-98.31
CAKI-1	-33.06
RXF 393	-19.84
SN12C	-71.22
TK-10	123.30
UO-31	-93.27
Prostate Cancer	
PC-3	24.63
DU-145	-80.22
Breast Cancer	
MCF7	-57.77
MDA-MB-231/ATCC	-75.12
HS 578T	-16.50
BT-549	3.34
T-47D	-50.20
MDA-MB-468	-81.08
Mean	-16.49
Delta	81.82
Range	221.61

Mean Growth Percent - Growth Percent

150 100 50 0 -50 -100 -150

Developmental Therapeutics Program

One Dose Mean Graph

AQQ9

Panel/Cell Line	Growth Percent
Leukemia	
CCRF-CEM	14.82
HL-60(TB)	10.31
K-562	3.49
MOLT-4	35.40
RPMI-8226	2.88
SR	23.98
Non-Small Cell Lung Cancer	
A549/ATCC	29.88
EKVX	65.02
HOP-62	89.07
HOP-92	110.14
NCI-H226	35.39
NCI-H322M	85.02
NCI-H460	78.80
NCI-H522	23.36
Colon Cancer	
COLO 205	111.51
HCT-116	13.11
HCT-15	32.37
HT29	97.02
KM12	80.01
SW-620	28.34
CNS Cancer	
SF-268	80.91
SF-295	70.12
SF-539	80.68
SNB-19	71.65
SNB-75	68.65
U251	60.26
Melanoma	
MALME-3M	83.76
M14	44.75
MDA-MB-435	-70.61
SK-MEL-2	47.23
SK-MEL-28	63.14
UACC-257	1.85
UACC-62	87.11
Ovarian Cancer	
IGROV1	22.08
OVCAR-3	3.53
OVCAR-4	22.64
OVCAR-5	109.50
OVCAR-8	57.16
Renal Cancer	
786-0	68.45
A498	71.38
ACHN	50.12
CAKI-1	75.25
RXF 393	73.06
SN12C	31.89
TK-10	119.08
UO-31	50.32
Prostate Cancer	
PC-3	57.92
DU-145	22.51
Breast Cancer	
MCF7	-56.67
MDA-MB-231/ATCC	45.82
HS 578T	43.11
BT-549	58.73
T-47D	3.43
MDA-MB-468	-9.52
Mean	47.76
Delta	118.37
Range	189.69

Mean Growth Percent - Growth Percent

150 100 50 0 -50 -100 -150

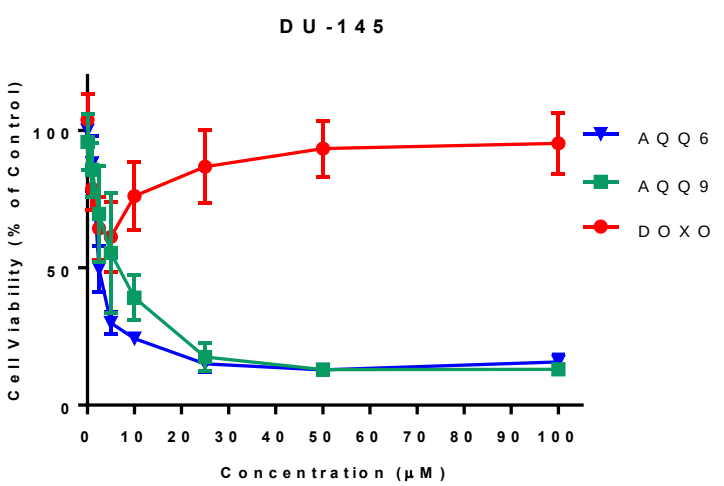
These data encoruged us to check anticancer activity and cancer sellectivity with several cell lines

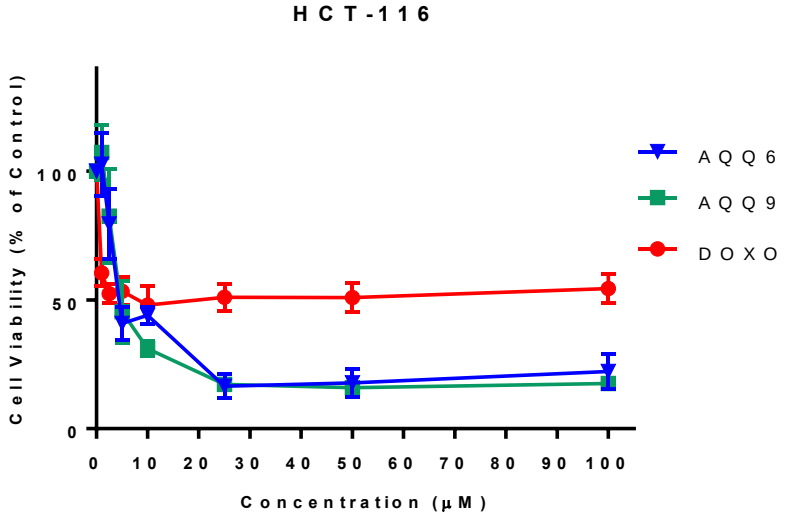
Results and discussion

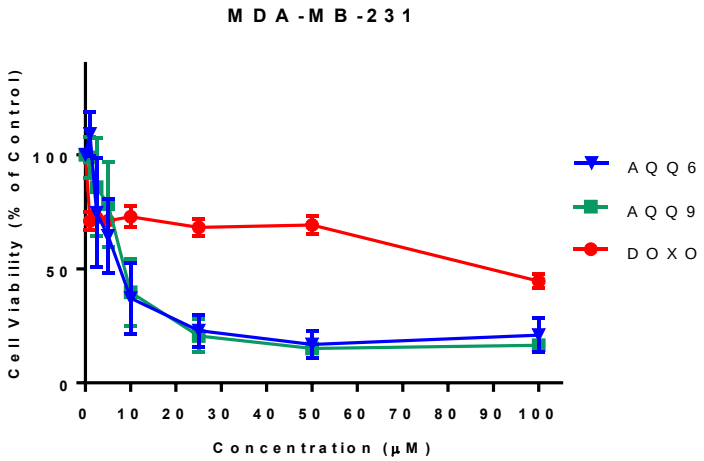
Cell lines	Breast cancer MDA-MB-231
	Colon cancer HCT116
	Prostate cancer DU145
	Healthy control HUVEC

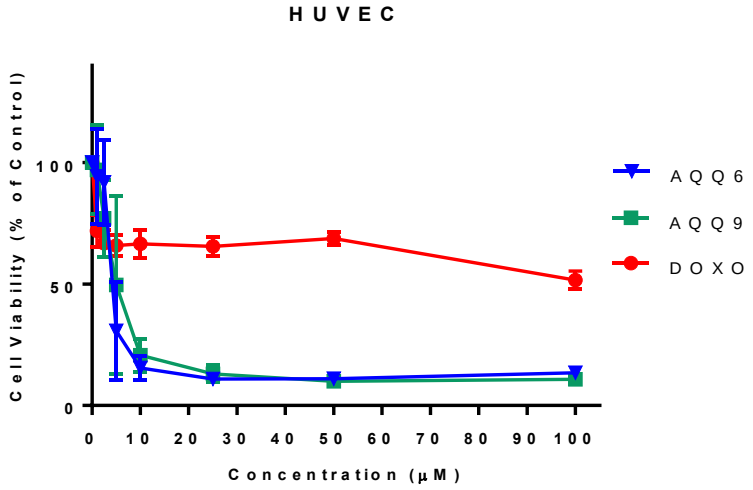
Between 0-100 µM 24 h exposure and cell viability by MTT test.

Results and discussion









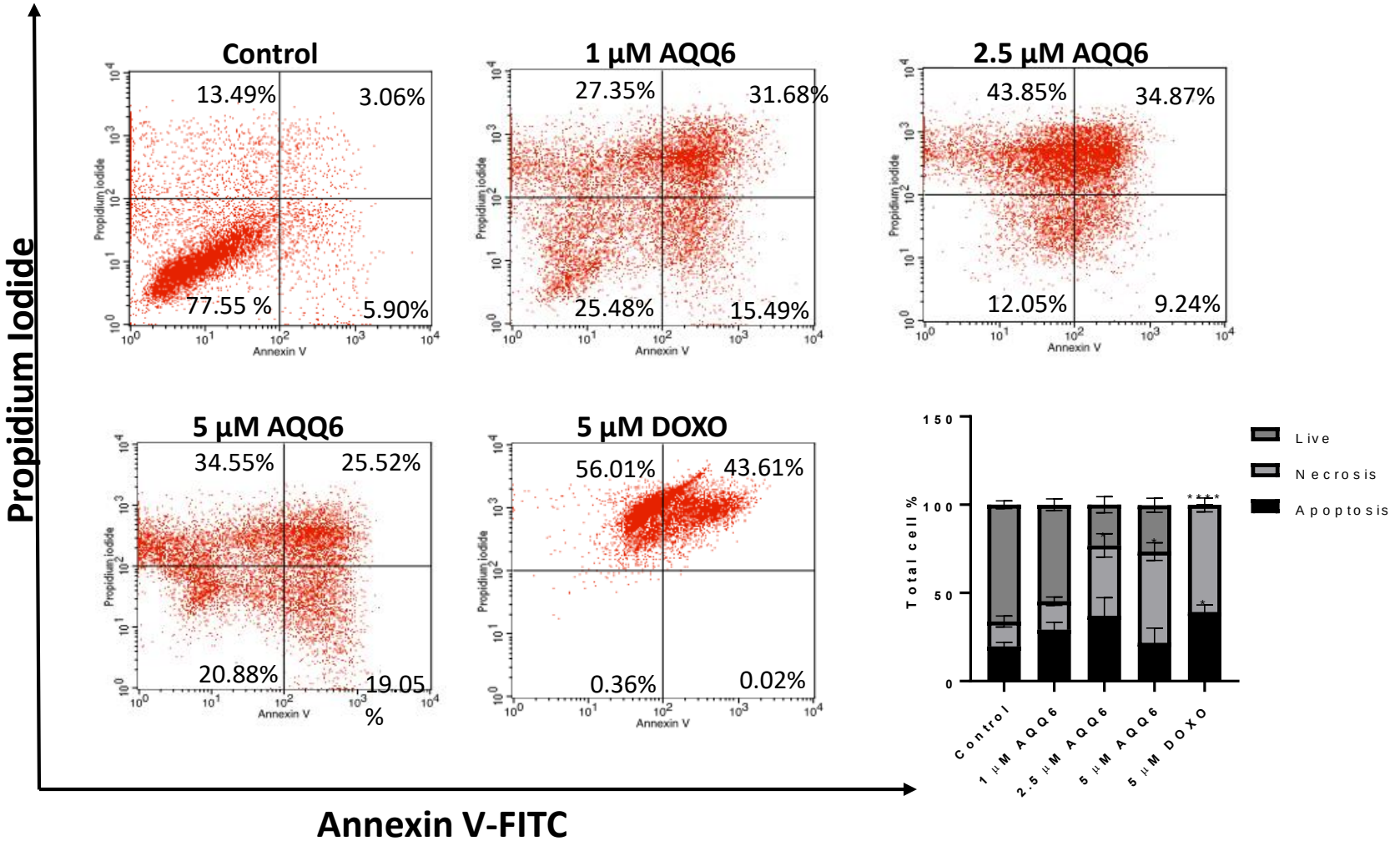
Results and discussion

	(μM)	DU-145	MDA-MB-231	HCT-116	HUVEC
AQQ6	IC_{50}	3.13± 0.15	9.05± 3.69	7.09± 1.35	5.17 ±0.16
AQQ9	IC_{50}	6.51±2.35	10.54± 3.87	6.64± 1.77	5.73± 2.15
DOXO	IC_{50}	< 100	61.74± 2.59	14.72± 2.65	81.9± 16.97

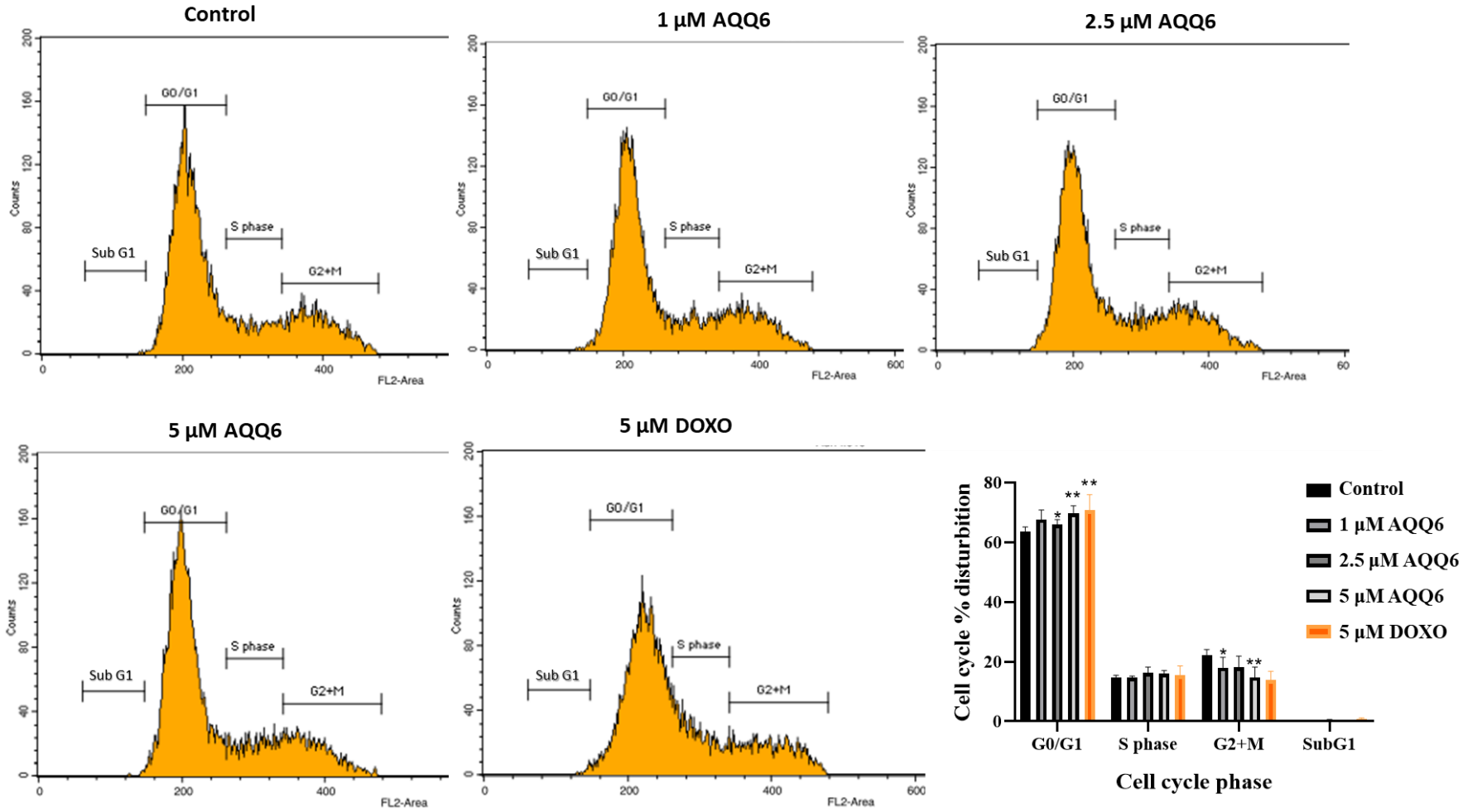
Effects of AAQ6 and AAQ9 on the growth of DU-145 prostate cancer, MDA-MB-231 breast cancer, HCT-116 colon cancer and and HUVEC non-cancerous cell line after 24h treatment by MTT assay.

IC_{50}: The compound concentration required to inhibit cell viability by 50%. The values are expressed as the mean ± SD.

Results and discussion



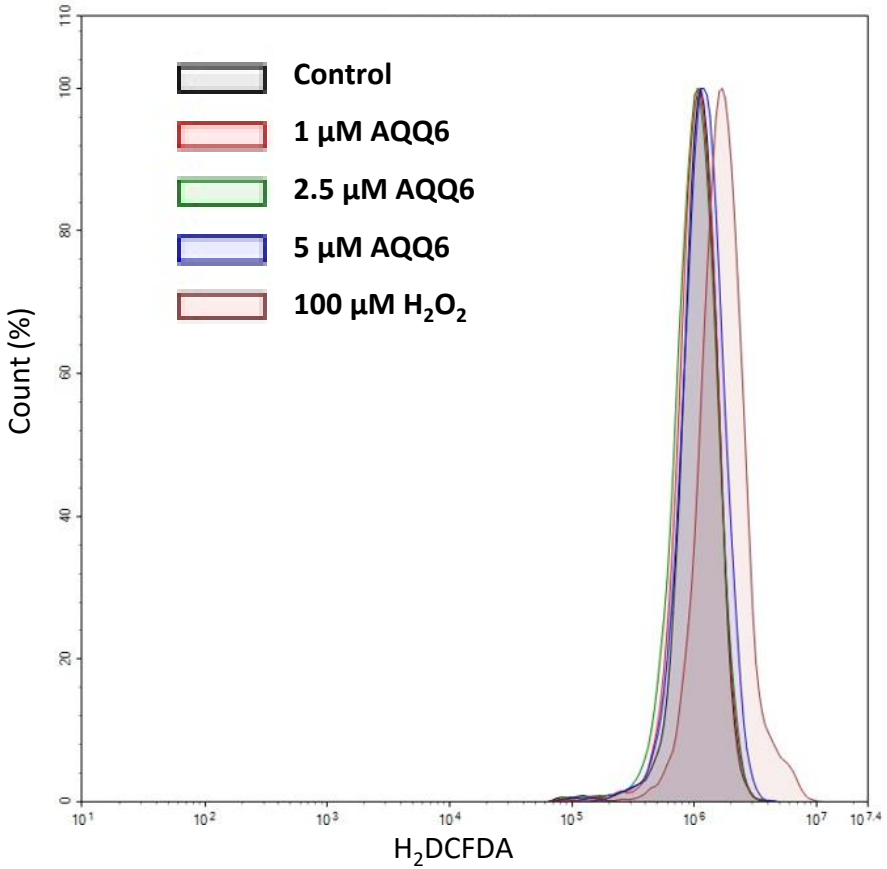
Results and discussion

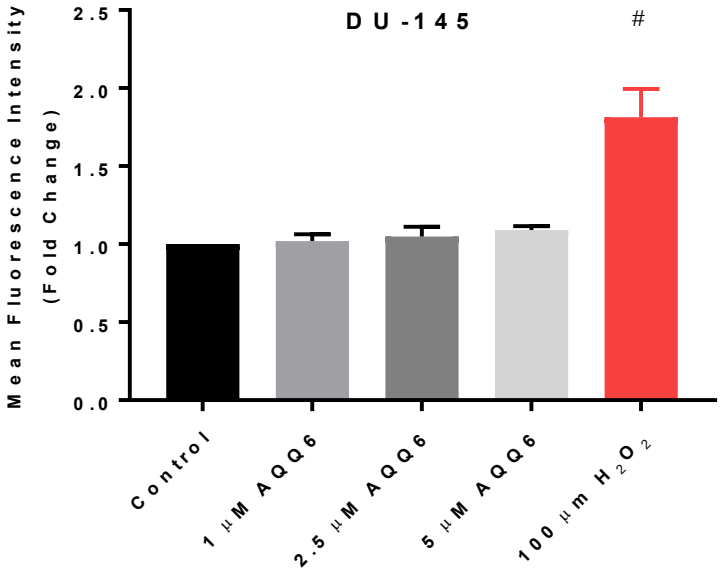


AQQ6 induced G0/G1 cell cycle arrest dose-dependently.

Results and discussion

ROS level measured by flow cytometry using H_2DCFDA staining





Results and discussion

- EDG is essential for biological potency of aminated quinolinequinones.
- Different donor group(s) (EDG, strong (OCH_3), or weak (CH_3)) caused different level of anticancer activity.
- Having a weak donor group resulted in stronger antiproliferative effects.
- AQQ6 which carries a methyl substituent was the most active compound and had good selectivity for DU-145 prostate cancer cells.
- Further studies showed that, AQQ6 caused dose dependent G0/G1 cell cycle arrest in DU-145 prostate cancer cells.
- AQQ6 caused apoptotic and necrotic cell death.
- Anticancer activity is not dependent on ROS production.
- In a recent study our group screened AQQ1-15 for their cytotoxic effects on leukemia cell lines. Similarly, weak EDG containing compounds showed higer cytotoxicity and AQQ13 showed the most promising anticancer profile against K562 leukemia cells thorough leading apoptosis.

10.1016/j.bioorg.2021.105160

Conclusions

- Aminated quinolinequinones can be promising structures in the drug development for cancer chemotherapy.
- AQQ6 compels attention as a potent and selective drug candidate for further anticancer research especially in prostate cancer.

Acknowledgments

This study is supported in part by the Istanbul University Research Fund. Grant no:TAB-2021-37247

Thank you for listening!