5-aminosalicylate–4-thiazolinone hybrid derivatives: A potent modulator of DNA damage response and G2/M cell cycle arrest via ATM/ATR pathway and Cyclin-CDK complex

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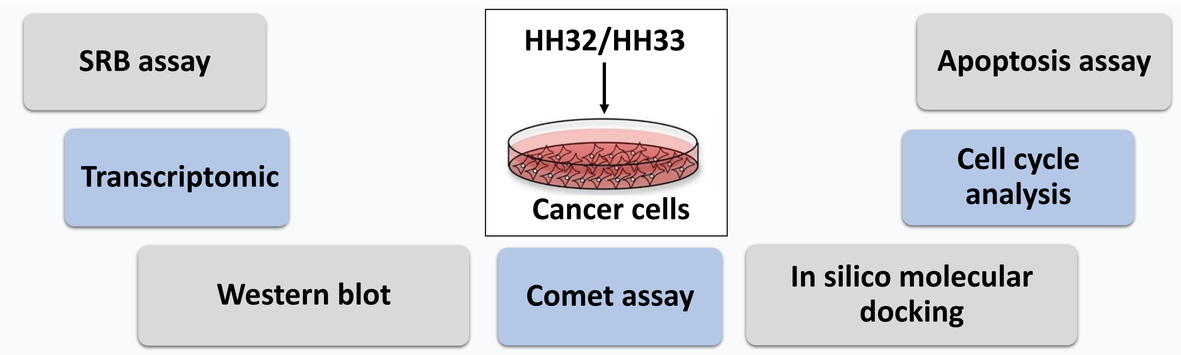
Introduction

The last several years have witnessed a tremendous advance in the knowledge of DNA repair and cell cycle mechanisms for the purpose of increasing the treatment efficacy of radiotherapy and DNA damaging agents. Thereby, targeting DNA damage and repair pathways and cell cycle checkpoints become an attractive rational to optimize treatment strategies through identifying new targets[1]. However, the improved knowledge has increased the complexity of DNA damage response (DDR) and checkpoints pathways which extremely proved challenges in the development of cell cycle and DNA repair targeting drugs[2]. To this end, a novel approach of synthesizing new compounds has been recently introduced which involved accommodating two chemical entities that target several molecules into a single structure.

Aims

Here we combined 5-aminosalicylic acid and 4-thiazolinone, which both reported to affect DDR and cell cycle progression, in a single structural framework to generate two derivatives named as HH32 and HH33. The transcriptomic, *in silico*, and *in vitro* analysis have been used to uncover the anti-cancer potential of HH-32 and HH-33 compounds.

Methods



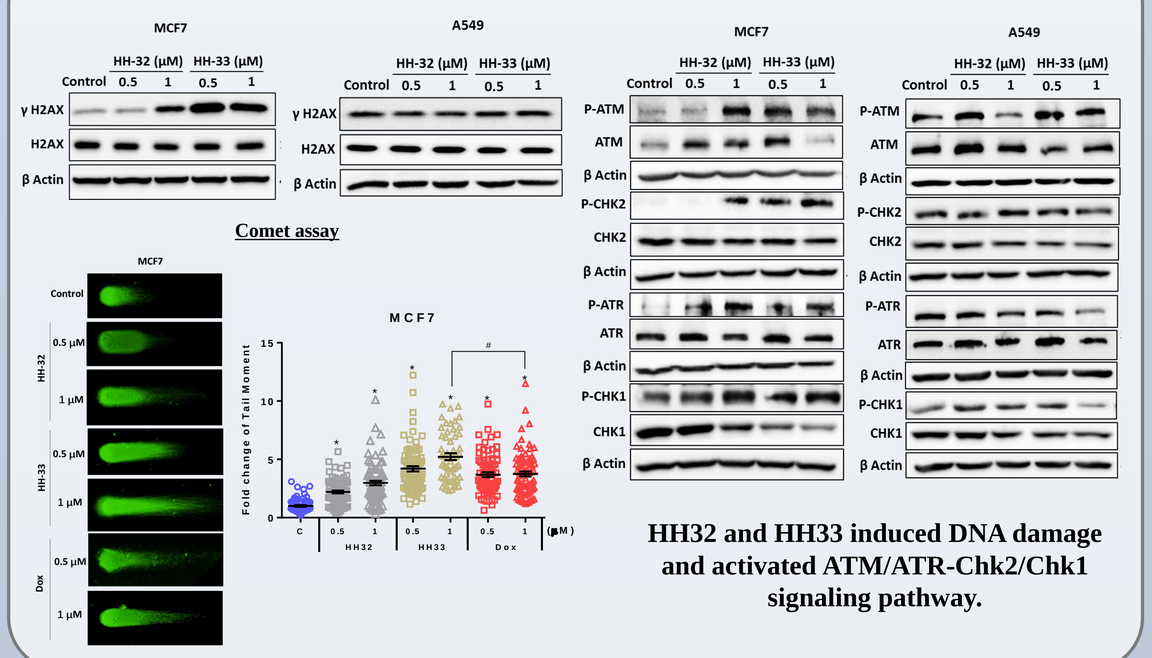
Results

1.1 HH-32 and HH-33 exhibited cytotoxicity towards cancer cells

	IC50 (µM)		
	HH32	HH33	Doxorubicin
MCF7	3.44 ± 0.32	0.81 ± 0.34	0.06 ± 0.38
HCT-116	1.17 ± 0.46	0.29 ± 0.47	0.11 ± 0.41
HeLa	0.60 ± 0.47	0.24 ± 0.51	0.46 ± 0.46
A549	6.17 ± 0.38	2.93 ± 0.83	0.62 ± 0.59
HepG2	2.49 ± 0.11	0.38 ± 0.11	0.37 ± 0.12
MDA-MB-231	15.35 ± 0.08	3.94 ± 0.08	0.45 ± 0.11
U87	6.53 ± 0.09	1.03 ± 0.11	0.10 ± 0.09
U373	29.38 ± 0.08	23.66 ± 0.08	0.88 ± 0.09
F-180	13.34 ± 0.38	3.91 ± 0.43	0.29 ± 0.37
HME1	26.79 ± 0.14	9.25 ± 0.14	1.12 ± 0.19

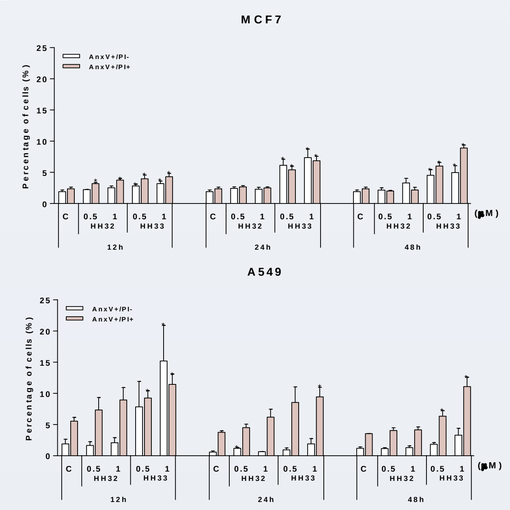
HH32 and HH33 exhibited an antiproliferative activity and good selectivity against a various types of cancer cells with lowest impact on normal cells.

1.3 HH-32 and HH-33 are potent DNA damage inducers



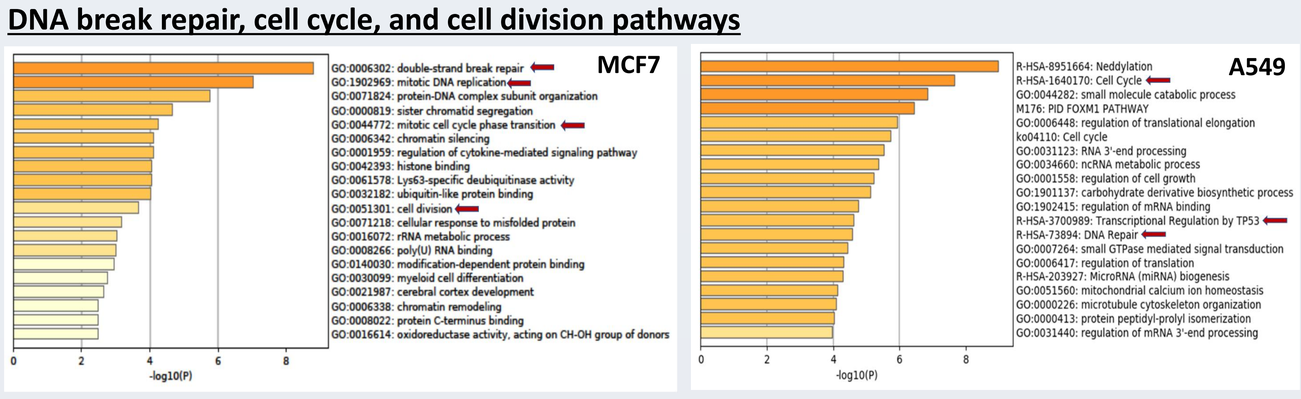
HH32 and HH33 induced DNA damage and activated ATM/ATR-Chk2/Chk1 signaling pathway.

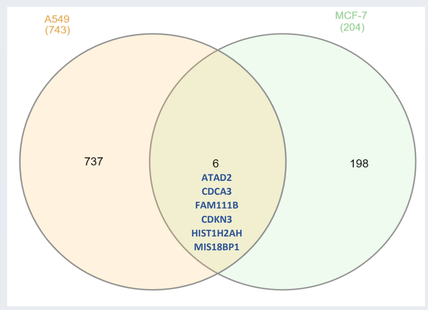
1.5 HH-32 and HH-33 triggered apoptosis



The early apoptotic cell population (AnxV+/PI-) of MCF7 cells was increased apparently after 24 and 48 h of HH33 treatment, while it was increased at earlier time (12 h) in A549 cells

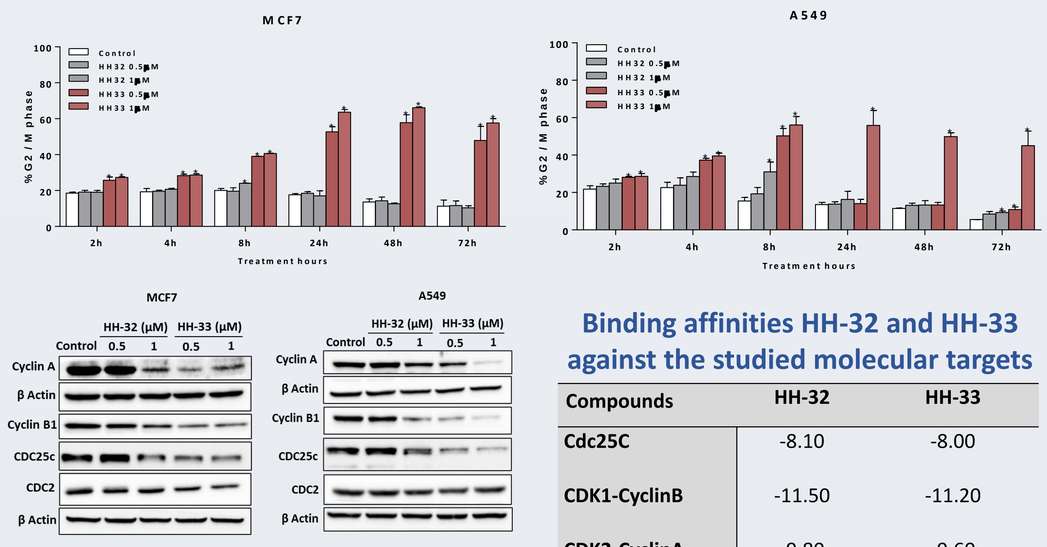
1.2 Transcriptomic Analysis of HH33-treated MCF7 and A549 cells showed downregulation of DNA break repair, cell cycle, and cell division pathways





Six shared Genes maximally downregulated in HH33-treated A549 and MCF-7 cells (ATAD2, CDCA3, FAM111B, CDKN3, HIST1H2AH and MIS18BP1) which involved in cell cycle, cell division and transcription.

1.4 HH-32 and HH-33 caused cell cycle arrest at G2/M phase

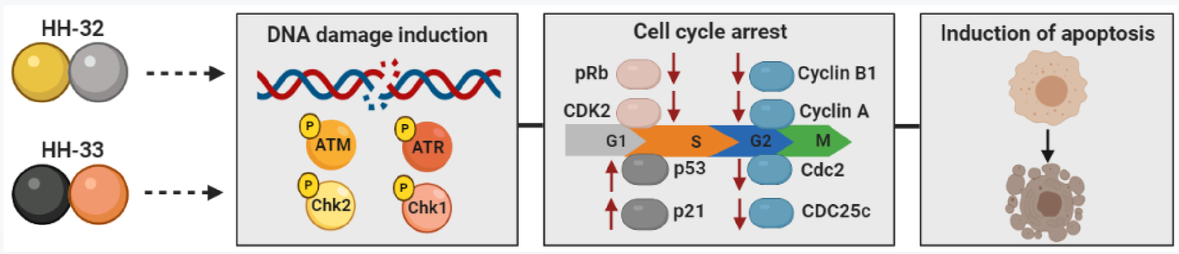


HH32 and HH33 upregulated CDK inhibitors, downregulated G2/M progression markers and ultimately arrest the cells at G2/M phase.

Binding affinities HH-32 and HH-33 against the studied molecular targets

Compounds	HH-32	HH-33
Cdc25C	-8.10	-8.00
CDK1-CyclinB	-11.50	-11.20
CDK2-CyclinA	-9.80	-9.60
Rb-Supressor	-10.10	-9.50

Conclusion



The pleiotropic biological effect of HH32 and HH33 compounds on cancer cells suggest the requirement for assessing their anti-cancer activities in preclinical models which may lead to a new area in the development of potential therapeutic drugs.

Acknowledgment

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References:

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2 Gavande, Navnath S *et al*. DNA repair targeted therapy: The past or future of cancer treatment?. *Pharmacology & therapeutics* **160,** 65-83 (2016). doi:10.1016/j.pharmthera.2016.02.003