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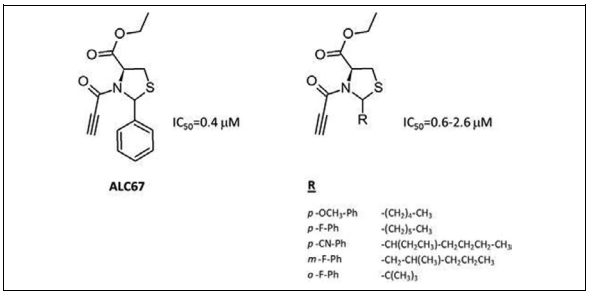
A novel thiazolidine molecules: Evaluation of their antiproliferative, mutagenic and genetoxic effects

Kerem Buran
Faculty of Pharmacy, Yeditepe University, Turkey

Cancer results from unregulated cell growth. Reactivating cell death in cancer cells, i.e. apoptosis, is a classical anticancer therapeutic strategy. Theapoptosis-inducerproperty of the (*2RS,4R*)-2-phenyl-3-propinoyl-thiazolidine-4-carboxylic acidethyl ester (ALC67) molecule has been discovered recently[1,2]. Toelucidate the mechanism of action of this molecule and to evaluate the impact of the phenyl group that the thiazolidine ring presents at its second position on thecytotoxicity, we developed derivatives ALC 67 analogues replacing the phenylmoiety with various aliphatic and aromatic groups.

Thecyto toxic activity of thenovel (*2RS,4R*)-2-phenyl-3-propinoyl-thiazolidine-4-carboxylic acidethyl ester derivatives were evaluated on humanliver HUH7 and Mahlavuhepato cellular carcinoma cell (HCC) lines with the sulforhodamine B (SRB) assay. Results demonstrated that the antiproliferative property was conserved when the phenylmoiety was replaced.

Since the mutagenic and genotoxic properties of marketed anticancer molecules constitute a main issue to be addressed, then we fosuced on the analysis of the mutagenecity, antimutagenecity and genotoxicity of ALC67 molecule which has promissing antiproliferative activity[3]. Themutagenicity and antimutagenicity of ALC67 were evaluated by Ames test performed on *Salmonella* TA98 and TA100 strains. Thegenotoxicity of this molecule was investigated in the chromosomalaberrationassay on humanlymphocytes. All results revealed that the analyzed structure is not mutagenic in two *Salmonella* strains tested and was not genotoxic in humanly mphocytes*in vitro*. All these results indicate that after performing some more mutagenicityassay using other recommended strains, this compound can be safely used for the development of new structures exhibiting anticancer activities.



	R		Yield (%)	Huh7 IC_{50} µM	MV IC_{50} µM
	ALC 67			5.3 ± 0.9	0.4 ± 0.5
	p -OCH_3-Ph-	(**3a**)	89	1.4 ± 0.1	0.7 ± 0.2
	p -F-Ph-	(**3b**)	37	0.7 ± 0.2	0.4 ± 0.2
	m -F-Ph-	(**3c**)	58	1.4 ± 0.4	1.7 ± 2.0
	o -F-Ph-	(**3d**)	30	1.7 ± 0.4	1.7 ± 0.6
	p -CN-Ph-	(**3g**)	24	2.6 ± 0.6	2.4 ± 2.3
	-$(CH_2)_4CH_3$	(**3h**)	55	1.8 ± 0.4	2.0 ± 1.4
	-$(CH_2)_3CH_3$	(**3i**)	87	0.5 ± 0.1	0.4 ± 0.1
	-$CH(CH_2CH_3)CH_2CH_2CH_2CH_3$	(**3j**)	30	1.7 ± 0.3	1.6 ± 0.2
	-$CH_2CH(CH_3)CH_2C(CH_3)_3$	(**3k**)	55	1.6 ± 0.4	1.1 ± 0.6
	-$CH(CH_3)CH_2CH_2CH_3$	(**3l**)	63	0.6 ± 0.3	0.5 ± 0.1
	-$C(CH_3)_3$	(**3m**)	52	0.8 ± 0.1	0.9 ± 0.1
	CPT			0.1	<1
	5FU			30.7	10.0