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Drug Candidates for Heat Shock Protein 90 Inhibition

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Organisms produce molecular machines-proteins to perform their functional roles. These machines have finely tuned structures for their biochemical roles. Environmental factors determine the structural characteristics of the proteins. Structural perturbations on proteins may lead activity enhancement and/or degradation. Therefore, organisms protect intact structure of the proteins universally through expressing a variety of Heat Shock Proteins (HSPs).

HSPs co-operate and/or coordinate with co-chaperones and/or partner chaperones [1,2]. HSPs are conserved among organisms and expressed constitutively or inducibly [3]. HSPs are present at different parts of a cell such as endoplasmic reticulum, cytosol, and mitochondria.

Why a cell needs redundant HSPs has been investigated several years and yet the molecular mechanism needs to be elucidated? However, several researches indicate that the coordination-cooperation of HSPs may bear specific cellular function [4].

HSPs are classified according to their molecular mass; Hsp70, Hsp40, Hsp90, Hsp100, Hsp60, nucleotide exchange factors and small Hsps. Details of the specific HSPs function may be found in recent reviews and my lab is currently focused on HSP90 and its inhibition [4].

HSP90 family is the most abundant cytoplasmic protein (1-2%) in unstressed cells. The 90 kDa protein consists of highly conserved N-terminal domain (25 kDa) and highly conserved C-terminal domain (50 kDa). This homodimeric protein has two cytosolic isoforms in higher eukaryotes; α and β [4]. HSP90 N terminal domain binds and hydrolyzes ATP and transfer the energy to the C-terminal domain for function through a conformational shift in the protein structure. This typical chaperone activity is similar to other members of the family i.e. HSP70. But HSP90 does not display nascent protein folding activity like HSP70. However, HSP90 coordinates with HSP70 through HOP protein to fold the substrate proteins.

HSP90 is involved in cell cycle control, transcriptional regulation and signal transduction, and chromatin-remodeling pathways.

Why researchers interested in HSP90 is its client proteins which play critical roles in the cancer pathways. These proteins include transcription factors, signaling proteins, and apoptotic factors and an updated list can be found at (http://www.picard.ch/downloads/Hsp90facts.pdf) [5,6]. Further, cancer cells can survive in stressed cells by adaptive mutations, chromosomal rearrangements, and elevating expression level of HSP90. Therefore, a cancer cell may find alternative routes both genetically and epigenetically to overcome the stress affect as survival strategy. HSP90 inhibition is the best bet to overcome these hurdles. Inhibition of HSP90 functions affects multiple oncogenic pathways simultaneously and several inhibitors have been developed for this purpose. One HSP90 N-terminal inhibitor is Geldanamycin. The inhibitor interferes with ATP-binding property of HSP90 and draws the attention of several research groups. Several Geldanamycin derivatives are in clinical trials for different cancer types [5,6].

One of the projects in my lab is C-terminal HSP90 inhibitors in collaboration with Dr. Irfan Koca research group. These coumarine based inhibitors (Figure 1) have been tested at a variety of cancer cell lines to test the toxicity. A parallel molecular docking study is underway to determine the key residues involved in HSP90 protein.

Results of HSP90 inhibition will be evaluated at molecular level and potential inhibitors will be a good start for drug development.

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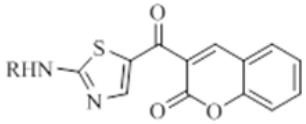
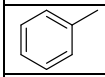
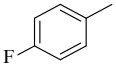
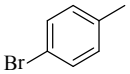
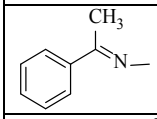
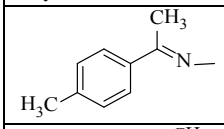
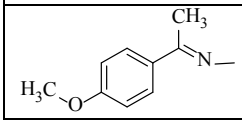
Figure 1: Coumarine derivative skeleton where R group is given below;



R-	Molecule Name	Molecule Formula
H_3C—	3-(2-(methylamino)thiazole-5-carbonyl)-*2H*-chromen-2-one	$C_{14}H_{10}N_2O_3S$
CH_3CH_2—	3-(2-(ethylamino)thiazole-5-carbonyl)-*2H*-chromen-2-one	$C_{15}H_{12}N_2O_3S$
	3-(2-(phenylamino)thiazole-5-carbonyl)-*2H*-chromen-2-one	$C_{19}H_{12}N_2O_3S$
	3-(2-(4-fluorophenylamino)thiazole-5-carbonyl)-*2H*-chromen-2-one	$C_{19}H_{11}FN_2O_3S$
CH_2=$CHCH_2$—	3-{[2-(allylamino)-1,3-thiazol-5-yl]carbonyl}-2*H*-chromen-2-one	$C_{16}H_{12}N_2O_3S$
	3-(2-(4-bromophenylamino)thiazole-5-carbonyl)-*2H*-chromen-2-one	$C_{19}H_{11}BrN_2O_3S$
	(Z)-3-(2-(2-(1-phenylethylidene)hydrazinyl)thiazole-5-carbonyl)-*2H*-chromen-2-one	$C_{21}H_{15}N_3O_3S$
	(Z)-3-(2-(2-(1-p-tolylethylidene)hydrazinyl)thiazole-5-carbonyl)-*2H*-chromen-2-one	$C_{22}H_{17}N_3O_3S$ (403.45)
	(Z)-3-(2-(2-(1-(4-methoxyphenyl)ethylidene)hydrazinyl)thiazole-5-carbonyl)-*2H*-chromen-2-one	$C_{22}H_{17}N_3O_4S$ (419.45)