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NUOVE PROSPETTIVE IN CHIMICA FARMACEUTICA

ABSTRACT BOOK

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Design and synthesis of high affinity compounds for the Hsp60 expression control in carcinogenic processes

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First observed in cells exposed to high temperatures, Heat shock proteins (Hsps) are nowadays considered the most important cell "chaperone" complexes over-expressed in response to a number of cell stress stimuli.[1] The chaperone activity is the main function of the eukaryotic Heat shock protein 60 kDa (Hsp60), involved in the capture and refold of unfolded or misfolded proteins. Additional roles in signal transduction,[2] senescence activation[3] and apoptosis[4] have been ascribed to cytosolic Hsp60. During the carcinogenIc process, *in vivo* studies demonstrated increased levels of human Hsp60 in several organs, such as uterine exocervix,[5] large bowel,[6] and prostate.[6]
In this context, our study aims to elucidate the structural details of the interaction between Hsp60 and novel designed antagonists able to specifically block this chaperonine. A preliminary virtual screening of 24 million molecules, available in the Zinc database, was carried out on the ATP-binding site of a bacterial Hsp60 monomer, the coordinates of which were taken from Protein Data Bank (ID: 1WE3), figure 1. Compounds with high affinity were further refined by other *in silico* protocols previously and successfully applied by us in the study of several biological targets.[7]

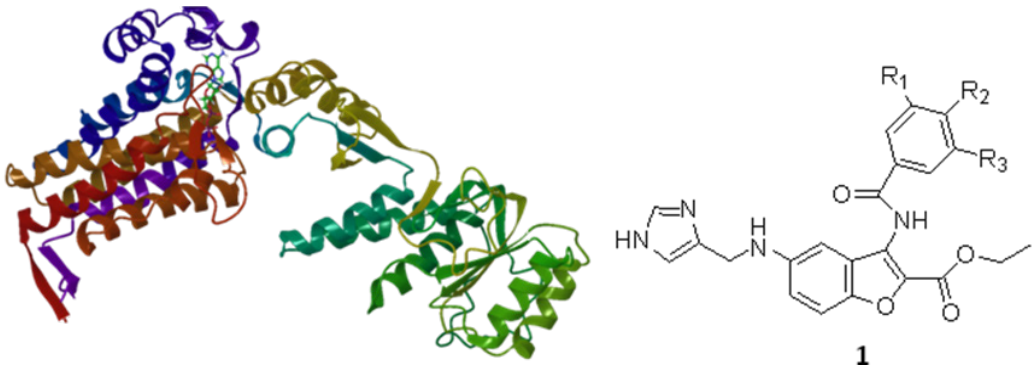

Figure 1. Bacterial Hsp60 monomer (left), selected benzofuran core structure (right).

The analysis of virtual screening results highlights the N-{5-[1H-imidazol-4-yl-methyl)-amino]-benzofuran-3-yl}-benzamides of type **1** as interesting series for the inhibition of Hsp60 ATP-binding site. Selected compounds were prepared in excellent yields, following appropriate synthetic pathways. All compounds are currently tested in order to proof they potential anticancer activity as modulator of Hsp60 function in tumor cells.

References

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