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ABSTRACT BOOK

NOVEL ANTAGONISTS FOR AN Hps60-BASED ANTICANCER CHAPERONOTHERAPY

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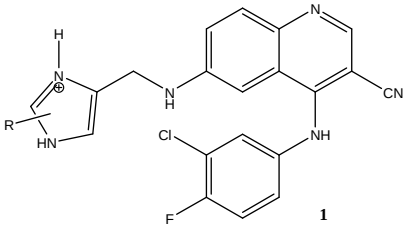
Unfolded or misfolded proteins may interfere with the machinery of the cell [1]. For this reason, eukaryotic and prokaryotic cells have evolved special macromolecular "chaperone" complexes that capture and refold partially folded proteins. The Heat shock proteins (Hsps) are nowadays considered the most important cell chaperones, which result overexpressed in response to a number of cell stress stimuli [2]. The chaperone activity is the main function of the eukaryotic Heat shock protein 60 kDa (Hsp60); nevertheless, additional roles in signal transduction [3], senescence activation [4] and apoptosis [5] have been ascribed to cytosolic Hsp60. *In vivo* studies have shown that levels of human Hsp60 increase during carcinogenetic steps [6,7]. In tumor cells, when Hsp60 accumulates in the cytosol, without mitochondrial release, it exerts an anti-apoptotic effect, by inhibiting pro-caspase-3 (pC3) activation [5].
In this context, our study aims to elucidate the structural details of the interaction between Hsp60 and pC3 and to design novel antagonists able to specifically block this interaction. 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, whose coordinates were taken from X-ray crystallography (PDB_ID: 1WE3). Nearly 25000 compounds were selected, with high affinity for the pertinent site of the bacterial Hsp60. These compounds will be further refined by other *in silico* protocols previously applied by us in the study of other biological targets [8].



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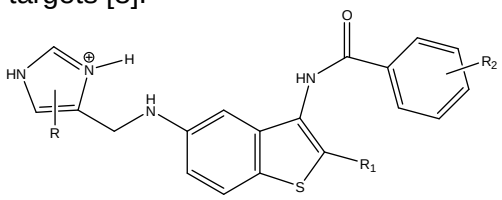

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The analysis of virtual screening results highlights the 4-(3-chloro-4-fluoro-phenylamino)-6-[(1H-imidazol-4-yl-methyl)-3-carbonitrile-quinolines of type **1** and the N-{5-[1H-imidazol-4-yl-methyl)-amino]-benzo[b]thiophen-3-yl}-benzamides of type **2** as interesting series for the inhibition of Hsp60 ATP-binding site. Selected compounds were prepared in excellent yields, following appropriate synthetic pathways. All the compounds were biologically tested in order to proof they potential anticancer activity as inhibitor of Hsp60 function in tumor cells.

References

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