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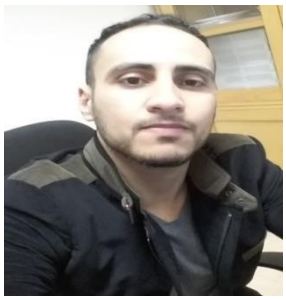
An Irreversible Inhibitor of HSP72 that Unpredictably Targets Lysine-56 –A molecular insight



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Abstract

HSP72, a stress-inducing molecular chaperone, is a significant therapeutic target in oncology, but it has proved particularly difficult to inhibit this protein with small molecules owing to competition with the high affinity and abundance of its endogenous nucleotide substrates. Recently, unexpectedly 8-N –benzyladenosine inhibit the HSP 72 by targeting the lysin 56 instead of cyst 17. This prompted us to investigate the dynamic behind this novel drug combination. To get insight into the observed un expected interaction, molecular dynamics simulations have been employed to investigate the inhibitory mechanism as well as the structural dynamics that characterize this effect. Structural dynamic analyses indicate that the lysine bound complex has shown a more compact and stable protein conformation compared to cysteine bound complex. In addition, binding free energy calculation suggests that van der Waals energy interactions were observed to be the main energy component driving this unanticipated effect. Furthermore, per-residue energy decomposition analysis identified Tyr 40, Glu 267, and Thr 264 as key residues that contribute largely to this unpredicted effect. The findings highlighted in this study provide a molecular understanding of the dynamics and mechanisms that mediate the new drug design paradigm for HSP72 chemical probes in oncology treatment.

Biography:

Aimen Aljoundi has completed his M.sc of pharmacy from Durban, University of KwaZulu-Natal School of Health Sciences, South Africa, currently his currying his PhD in Molecular Bio-Computation & Drug Design Lab He has published more than 2 papers in reputed journals.

Speaker Publications:

1. Covalent Versus Non-covalent Enzyme Inhibition: Which Route Should We Take? A Justification of the Good and Bad from Molecular Modelling Perspective; Protein J, 2020 Apr;39(2):97-105.
2. 'Piperazining' the catalytic gatekeepers: unraveling the pan-inhibition of SRC kinases; LYN, FYN and BLK by masitinib; Future Med Chem, 2019 Sep;11(18):2365-2380.
3. Turning to Computer-aided Drug Design in the Treatment of Diffuse Large B-cell Lymphoma: Has it been Helpful?; Anticancer Agents Med Chem,2019;19(11):1325-1339

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