CONFORMATIONAL SAMPLING OF SOME DUAL CK2/HDAC INHIBITORS

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The development of multi-target inhibitors is the modern dynamically expanding direction in drug design. Dual CK2/HDAC inhibitors are recognized as a novel therapeutic anticancer strategy aimed to increase the effectiveness of anticancer therapy [1, 2]. Conformational sampling of drug-like molecules is the necessary preliminary stage in rational drug design focusing on their structure organization, energetic penalties associated with undesired flexibility minimization, and finding optimal arrangement of the functional groups that interact with the protein binding site [3]. This stage is of key importance in case of dual inhibitors with a flexible long linker between two pharmacophoric groups. The aim of the present study was to perform a conformational sampling for dual CK2/HDAC inhibitors in a polar aqueous environment, to evaluate conformational ensembles and to learn the essential regularities of molecular properties varying across the conformational space. Conformational search was performed for four dual CK2/HDAC inhibitors – 5-[[7-(2-aminoanilino)-7-oxo-alkyl]amino]benzo[c][2,6]naphthyridine-8-carboxylic acid derivatives, synthesized at the Department of Chemistry and Biochemistry, San Pablo CEU University, Madrid, Spain (Fig. 1).

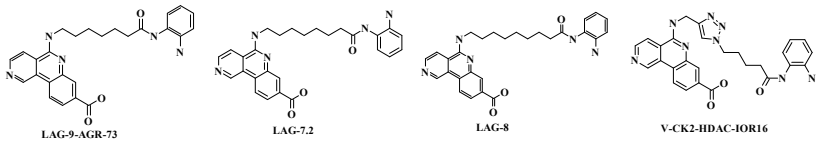

Fig. 1. Structures of dual CK2/HDAC inhibitors

To characterize the conformational ensembles, for each conformer four molecular properties were computed proven to be essential for cell permeability: volume of molecules, conformer shape (radius of gyration, R_{gyr}), polarity (Polar surface area, PSA) and the number of intramolecular hydrogen bonds (IMHB). The obtained results suggested that V-CK2-HDAC-IOR16 is the most stable compound as its conformations possessed the most compact structure with the lowest R_{gyr}, the lowest potential energy and the highest PSA.

The best conformations were selected for further MD simulations.

Acknowledgements: Financial support from MICINN for PID2021-123786OB-I00 project is kindly acknowledged. O. K. thanks Universidad San Pablo CEU for a Postdoctoral Contract for Ukrainian Researchers 2022–2024.

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