MOLECULAR DOCKING AND DYNAMICS SIMULATION OF SOME DUAL CK2/HDAC INHIBITORS TARGETING HISTONE DEACETYLASE1

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Histone deacetylases (HDACs) are a family of epigenetic proteins that control gene transcription and regulation, alongside cell proliferation, differentiation, migration, death, and angiogenesis [1]. Histone deacetylase inhibitors (HDACi) have vast potential as therapeutic agents for the treatment of cancer and have demonstrated anticancer efficacy across a range of cancers, most impressively in haematological malignancies [2]. One of the rapidly growing fields of research in anticancer therapy is the construction of dual HDAC/kinase inhibitors, a few of them are currently in preclinical and clinical trials [3]. Some novel CK2/HDAC inhibitors were synthesized at the Department of Chemistry and Biochemistry, San Pablo CEU University, Madrid, Spain, through combining the distinct pharmacophores of Tucidinostat and CX-4945. The objective of the present study was to perform molecular dynamic (MD) simulations on molecular docking results for two dual CK2/HDAC inhibitors (Fig. 1) to establish more reliable binding modes and analyse ligand-protein interactions.

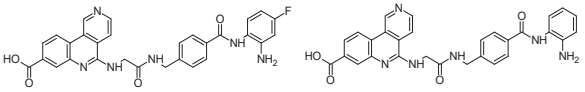

Fig. 1. Structures of dual CK2/HDAC inhibitors

The molecular docking was performed against HDAC1 (PDB: 4BKX) protein using Glide software of the Schrodinger suite [4]. The histidine His140, close to the active site of HDAC1, was protonated at the delta position (HID140). A python-based metal centre parameter builder (MCPB) [5] was utilized to parameterize metal ions centres. The generated protein-ligand complexes were subjected to 100 ns molecular dynamics (MD) simulation using Amber 22 suite [6].

The MD trajectory analysis included the RMSD assessment in the atomic positions of the ligands and backbone of the protein, fluctuations in the binding site evaluation and a per-residue energy decomposition procedure using the MMPBSA module of Amber. The obtained results allowed us to make conclusions concerning the stability of ligand-protein complexes and gave insight into protein-ligand interactions.

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