INHIBITION OF CASEIN KINASE 1 USING COMPUTATIONAL TOOLS

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In recent years, there has been widespread use of computer methodologies in research to discover new drugs. In the present study, efforts were made, with the use of computational methods, to discover molecules with inhibitory activity against the four Casein Kinase 1 (CK1) isoforms. Those kinases constitute major pharmacological targets for treating various pathologies. The mentioned family of kinases are a type of evolutionarily conserved monomeric serine threonine protein kinases that phosphorylate serine/threonine residues and differ significantly from Casein Kinase 2. Family of CK1 is partially responsible for many types of cancer, inflammatory diseases as well as in various neurodegenerative diseases of the Central Nervous System.[1]

The search of CK1 inhibitor candidates was conducted in four open access molecule databases. Three different highly potent and reliable algorithms were used for the virtual screening process. Firstly, a theoretical model was constructed and validated with the use of available experimental data. Consequently, structure-based methods, as well as ligand-based methods, were applied. Binding and valuation calculations were used at two levels of protein modulation accuracy. In addition, a virtual evaluation was performed by comparing the three-dimensional structural similarity between the molecules under study and known inhibitors of the investigated kinases (ligand-based). Finally, the results obtained through the different techniques mentioned were compared and a group of molecules with high probability of being biologically active against the CK1 kinases were selected.[2] The binding of these lead compounds to the target kinases was studied by molecular dynamics simulations to draw conclusions about the time-dependent dimension of the interaction. Compounds that exhibit optimal characteristics and potential promising biological activity will be tested experimentally as potential inhibitors of the aforementioned proteins.

[1] Y. Qiao et al., *Small molecule modulators targeting protein kinase CK1 and CK2*, Eur. J. Med. Chem., **2019**, 181, 111581

[2] V. Myrianthopoulos, G. Lambrinidis, and E. Mikros, *In Silico Screening of Compound Libraries Using a Consensus of Orthogonal Methodologies*, Methods Mol. Biol., **2018**, 1824, 261