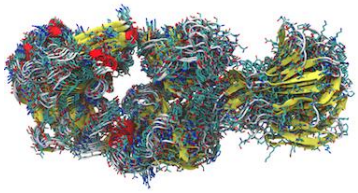

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Structural and conformational characterization of Nek1 protein and new pyrimidine inhibitors with therapeutic potential in the treatment of glioblastoma

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Abstract: Gliomas are primary brain tumors accounting for 80% of all malignant brain tumors. Surgery, radiotherapy, and temozolomide (TMZ)-based chemotherapy are fundamental treatment options in clinical management. However, most gliomas are surgically unresectable and, when diagnosed at an advanced stage, such as glioblastomas (GBM), the level of resistance to conventional chemotherapy increases. Nek1 is one of the proteins that has been associated with tumor resistance in GBM cells. Due to its high expression in GBM and its relation to tumor aggressiveness, proliferation and chemotherapeutic resistance, Nek1 protein may represent a therapeutic target with high potential in the treatment of these tumors. Dihydropyrimidinones (DHPMs) are molecules that have been outstanding in recent decades for their bioactivity, such as antiviral, anti-inflammatory, antibacterial, antihypertensive and antitumoral. Considering the difficulty in the treatment of GBM, the present study proposes the search for new inhibitor(s) derived from DHPMs, targeting the Nek1 protein, through computational tools. The use of tools for identifying new drug candidates has provided substantial information regarding molecular recognition in receptor-ligand complex formation. For this, comparative modeling (Modeller v.9) was employed to produce a complete structure of Nek1. For molecular docking calculations, the AutoDock Tools software was used to prepare the receptor and ligand and AutoDock Vina software for the interaction energy calculations. The systems were submitted to molecular dynamics simulations (MD) using GROMACS and GROMOS54A7 force field. For DHPMs ligands, a protocol for parameter optimization combining *ab initio* and MD simulations was employed, and a fitting of the quantum-mechanical and molecular-mechanical potential energy profiles generated new torsional parameters. The quality of the Nek1 model was checked with Procheck, Verify 3D and MolProbity. MolProbity revealed through Ramachandran plot that 97.5 % of all residues were in favored (98 %) regions and 100% of all residues were in allowed regions. The docking calculations allowed the choose of the best eleven molecules to perform molecular dynamics studies. The eleven top scored ligands were selected from to perform MD simulations aiming to investigate the flexibility and stability of these complexes. In addition, Nek1 apoprotein structure and Nek1-ADP were also simulated as control. The present study aims to obtain information on the specificity of derivative DHPMs inhibitors in Nek1 protein using techniques of computational modeling, molecular docking and molecular dynamic simulations. It is expected that the data collected can contribute to the development of drugs with therapeutic potential in the treatment of GBM.