Competitive Inhibition of DNA Polymerase by XNA Nucleosides

Kim, Edward

Shingles, herpes zoster virus, affects many middle aged adults around the world, exhibiting symptoms of pain, itching, burning, and postherpetic neuralgia. In an attempt to discover effective new antiviral treatment solutions for this painful virus, investigation efforts were focused on the effects of XNA nucleosides, DNA analogs which provide potential for competitive inhibition, on DNA polymerase. The investigation was executed in two parts: laboratory experimentation and computational analysis. Using Real-time PCR, the laboratory experimentation revealed the inhibitive properties of the thymidine LNA nucleoside on Taq DNA polymerase. Further analysis of the LNA thymidine nucleoside revealed the competitive nature of the inhibition. The computational analysis corroborated the laboratory data by providing models of which to evaluate the binding affinity of the protein-ligand structure. The results of the Autodock Vina docking simulation, suggested similar binding affinities for the XNA nucleosides. Detailed analysis points to a distinct interaction between the LNA thymidine nucleoside and the ASP610 residue of the Taq polymerase molecule. In order to comprehensively evaluate the docking of LNA T nucleoside, the Gromacs molecular dynamics software was used to simulate the motion of the protein-ligand complex for 1000 picoseconds. The results of the simulation revealed substantial conformational change in the polymerase resulting in the inhibition. The investigation pointed to the high potential of the LNA thymidine nucleoside for future antiviral treatment. Further research and development of this drug may result in a promising solution for shingles and other threatening viruses.

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