Characterization of the Binding Pathways of Peramivir to H274Y Neuraminidase with Molecular Dynamic Simulations and MM/GBSA Analysis

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The influenza (flu) virus persists in causing widespread illness in the United States, infecting 5-20 % of the population each year. Its rapid mutation within various hosts such as birds, pigs and humans has led to influenza strains that have evolved resistance to commercial antiviral drugs such as oseltamivir. It has thus become desirable to develop a strategy to counter the continuous adaptations of influenza. Neuraminidase, a surface protein on the viral envelope, is essential for virus proliferation and is highly conserved across different strains. Close investigation of neuraminidase and its association characteristics with various existing antiviral drugs presents an opportunity to characterize the enzyme in a more detailed manner and potentially achieve significant acceleration of drug design. To advance towards this goal, we have studied the binding pathways of peramivir onto the active site of the H274Y mutant of neuraminidase with a multiscale computational approach. Thirty-three ligand clusters representing different spatial approaches were identified using Brownian Dynamics simulations on predetermined ellipses around the active and secondary sites. From each of the clusters, representative ligand conformations were used to initiate molecular dynamic simulations. From the sampling provided by these simulations, Molecular Mechanics/Generalized Born Surface Area (MM/GBSA) calculations were performed to reveal the favorable binding pathways of the ligand to the active site.

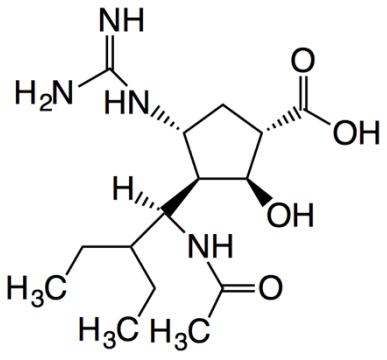

Figure 1. Chemical structure of peramivir