Investigation of Oseltamivir Binding Kinetics to N1 Influenza Neuraminidase

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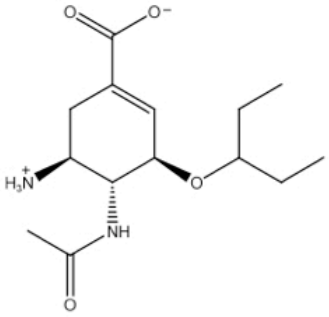
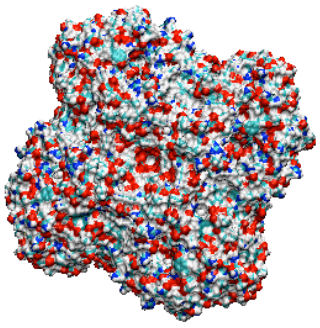
The ability of Influenza A to spread and infect new host cells is dependent on the cleavage of its tether to the host cell by the neuraminidase enzyme (NA). The site of cleavage is a sialic acid group located at the terminus of a host cell surface receptor, which can bind to both an active and a secondary site on NA. Drugs such as peramivir, zanamivir, and oseltamivir prevent the spread of the virus by binding to the active and secondary site of NA and acting as competitive inhibitors to sialic acid. Previous research by our group using Brownian Dynamics has shown oseltamivir to have an unusually high association rate constant to the active site of NA in comparison to zanamivir and peramivir as well as sialic acid itself, despite similarities in structure and size between all four molecules. This project investigated this surprising result after first remodeling the oseltamivir ligand *ab initio* using Gaussian geometric optimizations and AMBER RESP fitting. Small changes to the structure of oseltamivir, such as substituting the primary amine with a guanidinium group, were tested in further simulations elucidate the molecular features that give rise to oseltamivir's unique behavior.



Oseltamivir



Neuraminidase