Simulating the Binding Pathways of Sialic Acid and Oseltamivir to H274Y Neuraminidase with Molecular Dynamics Simulations

David F. Dacres, Erin M. Lewis, Richard W. Wenner, Jordan F. Graziadei,
and Adam W. Van Wynsberghe

Department of Chemistry, Hamilton College, Clinton, NY 13323

Neuraminidase (NA), a homotetrameric influenza capsid surface protein, recognizes and cleaves sialic acid moieties from host cell surface receptors to allow the virus to proliferate and infect other cells. This characteristic of NA has made it a vital target for antivirals to impede nascent virus release. A mutant strand of NA, H274Y, has shown to be resistant to oseltamivir, a commonly used NA competitive inhibitor. In this project, we have investigated how this mutant strand is resistant to oseltamivir while still maintaining its capabilities to bind to the natural substrate, sialic acid. To do so, we use a multi-scale simulation method that incorporates Brownian Dynamics (BD), Molecular Dynamics (MD), and Molecular Mechanics/Generalized Born Surface Area (MM/GBSA) free energy calculations to study the binding pathways of oseltamivir and sialic acid to the H274Y NA. First, BD is used to collect representative ligands that show the diffusional approach of the ligand to the protein. Then, these ligands were used to initiate MD trajectories to simulate proximal interactions between the ligand and the protein. Finally, MM/GBSA free energy analysis of the frames from the MD trajectories enables the elucidation of the key pathways the ligands take as they approach the active and secondary sites.

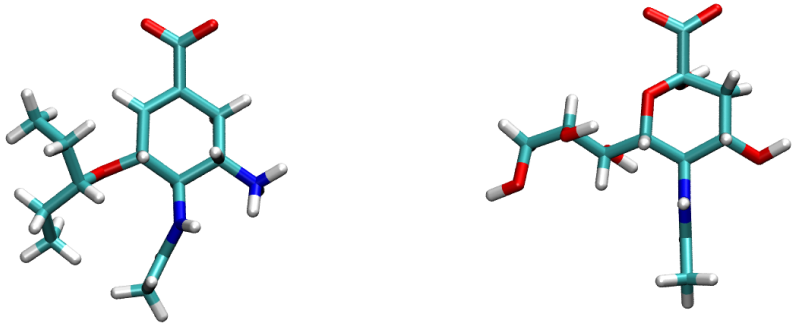

Figure 1. Oseltamivir (left) and Sialic Acid (right) with the carboxylate ion up