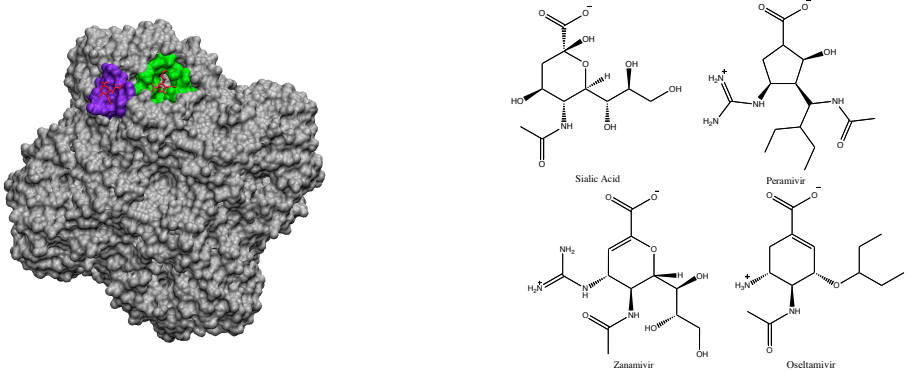
Association Rate Constants of Peramivir and Zanamivir to Influenza A Neuraminidase Active and Secondary Sites.

Erica L. Losito, Jeffrey C. Sung, Carlos A. Rico, and Adam W. Van Wynsberghe
Department of Chemistry, Hamilton College, Clinton NY 13323

The neuraminidase protein of the influenza A virus contains not only a catalytically active sialic acid binding site, but a secondary sialic acid binding site of unknown function. The active site acts to cleave terminal sialic acid moieties from cell surface receptors, allowing the release of new virus copies from the host cell. The spread of new virus copies can be blocked by neuraminidase inhibitors, such as peramivir and zanamivir, which give the body time to issue an immune response by binding to the neuraminidase and thereby blocking the binding of sialic acid. By running Brownian Dynamics (BD) simulations of the association of peramivir and zanamivir with two strains of the influenza A virus, we were able to compare the kinetics of the binding of these drugs to previous studies on the kinetics of the binding of sialic acid to the same neuraminidase sites. The association rate constants between the active and secondary site of each influenza strain and inhibitor were also compared. Both zanamivir and peramivir associated with the secondary site faster than with the active site of the same strain. Surprisingly, the association rates of zanamivir and peramivir showed greater similarity to those of sialic acid than those of oseltamivir despite close structural similarities between the three neuraminidase inhibitors. These findings and additional research could offer further insight into drug-flu interactions and assist in the effort to rationally design small-molecule inhibitors of neuraminidase.



Neuraminidase N1 tetramer (pdb: 2HTY) with sialic acid present in the active site (green) and the secondary site (violet); chemical structures of sialic acid and three neuraminidase inhibitors.