# Neuraminidase Inhibitor R-125489 – A Promising Drug for Treating Influenza Virus: Steered Molecular Dynamics Approach

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**Abstract.** Two neuraminidase inhibitors, oseltamivir and zanamivir, are important drug treatments for influenza. Oseltamivir-resistant mutants of the influenza virus A/H1N1 and A/H5N1 have emerged, necessitating the development of new long-acting antiviral agents. One such agent is a new neuraminidase inhibitor R-125489 and its prodrug CS-8958. An atomic level understanding of the nature of this antiviral agents binding is still missing. We address this gap in our knowledge by applying steered molecular dynamics (SMD) simulations to different subtypes of seasonal and highly pathogenic influenza viruses. We show that, in agreement with experiments, R-125489 binds to neuraminidase more tightly than CS-8958. Based on results obtained by SMD and the molecular mechanics-Poisson-Boltzmann surface area method, we predict that R-125489 can be used to treat not only wild-type but also tamiflu-resistant N294S, H274Y variants of A/H5N1 virus as its binding affinity does not vary much across these systems. The high correlation level between theoretically determined rupture forces and experimental data on binding energies for the large number of systems studied here implies that SMD is a promising tool for drug design.