How does oseltamivir lose its activity against virulent H5N1 mutants?

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An urgent issue is the emerging of the avian influenza A virus subtype H5N1. Since its first infection in Hong Kong in 1997, the highly pathogenic H5N1 has been shown to cross the species barrier and infect humans. The disease has caused many animal poultry and human deaths in various countries throughout the world. The important and growing problems of resistance to available anti-influenza drugs, oseltamivir and adamantane analogs, show the need for understanding in detail how these drugs interact with their enzyme target. Understanding of the molecular basis of drug binding and determininants affinity is needed to design and develop more potent inhibitors against both wild-type and mutant influenza strains. Here, we attempted to obtain the molecular details on the oseltamivir resistance to H274Y and N294S H5N1 mutants using molecular dynamics simulations [1]. The drug-target interactions were extensively analyzed in terms of intermolecular hydrogen bond lengths and particular distances in comparison between those obtained from two simulated mutant and wild-type systems [2]. Reduction of the hydrophobicity and size of pocket in the area around an ethyl moiety at the bulky group of oseltamivir were found to be the source of the resistance. These changes were primarily due to the dramatic rotation of the hydrophilic $–COO^-$ group of Glu276 toward the ethyl moiety. This leads to a reduction of the predicted binding affinity of oseltamivir against the mutants of influenza virus A virus.

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