

## **Structure-based drug discovery for influenza by targeting the cap-snatching endonuclease activity**

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An estimated 3-4 million severe illnesses and 500,000 deaths annually are associated with influenza. Seasonal influenza vaccines are targeted against dominant circulating strains of the virus, leaving those exposed to drifted or zoonotic strains at risk for infection. Most small molecule influenza drugs act as neuraminidase inhibitors or M2-ion channel inhibitors, and these drugs are becoming ineffective due to the emergence of resistance mutations. The viral RNA-dependent RNA polymerase (RdRp) has emerged as an attractive drug target: it is essential to viral replication and is better conserved than surface proteins. Using the recently determined crystal structure of the 'cap-snatching' endonuclease domain of the viral RdRp, and applying the structure-based drug discovery approach, we have developed a potent class of inhibitors based on the 5,6-dihydropyrimidine scaffold. These inhibitors show inhibitory activity against the purified enzyme in nanomolar range and in cell-based assays in micromolar range. Crystal structures of the protein-inhibitor complexes show the preferred binding modes for these compounds and reveal that the active site can undergo considerable reorganization upon inhibitor-binding. These structures provide opportunities for exploiting crucial interactions at the active site for improving the drug-like properties of these potent inhibitors.