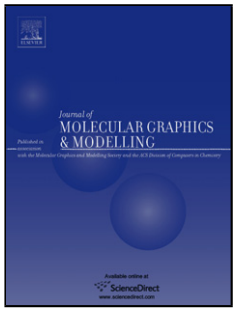

Title: Structure-based Methods to Predict Mutational Resistance to Diarylpyrimidine Non-nucleoside Reverse Transcriptase Inhibitors

Authors: Syeda Maryam Azeem, Alecia N. Muwonge, Nehaben Thakkar, Kristina W. Lam, Kathleen M. Frey

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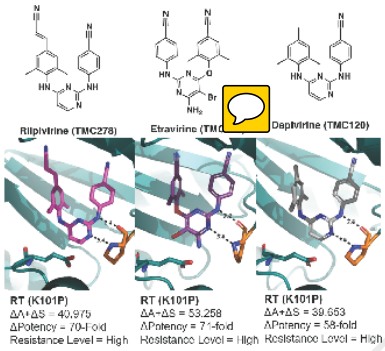
Graphical abstract

Graphic:



Abstract:
Resistance to non-nucleoside reverse transcriptase inhibitors (NNRTIs) is a leading cause of HIV treatment failure. Often included in antiviral therapy, NNRTIs are chemically diverse compounds that bind an allosteric pocket of enzyme target reverse transcriptase (RT). Several new NNRTIs incorporate flexibility in order to compensate for lost interactions with amino acid conferring mutations in RT. Unfortunately, even successful inhibitors such as diarylpyrimidine (DAPY) inhibitor rilpivirine are affected by mutations in RT that confer resistance. In order to aid drug design efforts, it would be efficient and cost effective to pre-evaluate NNRTI compounds in development using a structure-based computational approach. As proof of concept, we applied a residue scan and molecular modeling strategy using an RT crystal structure to predict mutations that confer resistance to DAPYs rilpivirine, etravirine, and investigational microbicide dapivirine. Our predictive values, changes in affinity and stability, are correlative with fold-resistance data for several RT mutants. Consistent with previous studies, mutation K101P is predicted to confer high-level resistance to DAPYs. These findings were further validated using structural analysis, molecular dynamics, and an enzymatic reverse transcription assay. Our results confirm that changes in affinity and stability for mutant complexes are predictive parameters of resistance as validated by experimental and clinical data. In future work, we believe that this computational approach may be useful to predict resistance mutations for inhibitors in development.