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Structure-Based Design of Dual inhibitors of HIV Integrase and Ribonuclease H

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Integrase (IN) inhibitors are the most recently developed class of antiretroviral agents with raltegravir, elvitegravir and dolutegravir being approved by the FDA. However, the emergence of drug-resistant IN mutants has emphasized a need to develop additional agents that have improved efficacies against resistant IN strains. Novel inhibitor scaffolds could perhaps overcome problems of resistance with existing IN inhibitors and could be useful antiretroviral agents to be used alone or in combination with existing anti-HIV agents. Highly active antiretroviral therapy (HAART) that combines single inhibitors targeting various stages of the viral life cycle has shown significant success. Multi-targeted single agents could provide the advantages of HAART such as lowered resistance while also circumventing the pharmacokinetic problems associated with HAART. Additionally, novel anti-HIV agents that target viral enzymes not yet explored could help alleviate resistance. The enzyme reverse transcriptase is responsible for the synthesis of double-stranded DNA starting from viral RNA and proceeds through an RNA/DNA hybrid intermediate. RNA removal is performed by the reverse transcriptase-associated ribonuclease H (RNase H). RNase H function is essential for viral replication and provides a novel therapeutic target for the development of antiretroviral agents. We have identified novel compounds with designed multi-targeted inhibitory attributes against IN and RNase H in silico. The synthesis for target compounds is underway and results from the molecular modeling study will be presented and discussed.

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