Structure-Based Design of New AIDS Drugs: Overcoming Drug Resistance

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Drug resistance is a primary cause of AIDS treatment failure. A multidisciplinary effort [1] led to the discovery of the potent diaryl-pyrimidine (DAPY) nonnucleoside inhibitors (NNRTIs) dapivirine, etravirine, and rilpivirine that are under clinical evaluation. Systematic structural and modeling studies of HIV-1 reverse transcriptase (RT) in complexes with NNRTIs used in the drug design effort revealed different modes of binding for the DAPY inhibitors [2]. The torsional flexibility ("wiggling") of the inhibitors can generate numerous conformational variants and the compactness of the inhibitors permits repositioning and reorientation (translation and rotation) within the pocket ("jiggling"). Such adaptations appear to be critical for the ability of the NNRTIs to retain their potency against a wide range of drug-resistant HIV-1 RTs. Exploitation of inhibitor conformational flexibility can be a powerful element of drug design, especially for the design of drugs that will be effective against rapidly mutating targets.

[1] Janssen P.A.J., et al., *J. Med. Chem*., 2005, *in press*. [2] Das et al., *J. Med. Chem.,* 2004, **47,** 2550.

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