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STRUCTURAL BASIS OF DRUG RESISTANCE TO HIV-1 PROTEASE INHIBITORS

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HIV-1 protease (HIV PR) has become an important target for the design of antiviral agents for AIDS. Several laboratories have recently produced HIV PR mutants in tissue culture under selection pressure using HIV PR inhibitors including the structurally-related C2 symmetry-based inhibitors, A-77003, A-84538, and P-9941. and two norstatine-containing compounds, KNI-272 and RPI-321. We have solved the atomic resolution structures of complexes of HIV PR with A-77003 and KNI-272 using X-ray crystallographic methods. Modeling studies based on these structures have been used to rationalize the effects of specific mutations on drug binding and cross resistance. Recently, we solved and refined the 2.25 Å resolution crystal structure of the recombinant V82A mutant of HIV PR complexed with A-77003. This mutant arose during resistance studies with A-77003 and P-9941. Comparison of the wild type and mutant enzyme complexes revealed asymmetric structural effects on enzyme/inhibitor interactions. Main chain shifts in the S1 subsite residues 79-84 resulted in a repacking of mutant enzyme and inhibitor atoms in an unexpected fashion. These structural results suggest strategies for the re-design of drugs that will specifically target subsite mutants of HIV PR.

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