

**P002** An alternative strategy for inhibiting multidrug-resistant mutants of the dimeric HIV-1 protease by targeting the subunit interface

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Mutations that occur in response to therapeutic antiproteases are responsible for the development of multidrug cross-resistances. This is one of the major limitations of the long-term treatment of AIDS patients. One alternative to inhibiting the homodimeric HIV-1 protease is to target the dimer interface of the enzyme at the antiparallel  $\beta$ -sheet formed by the interdigitation of the C- and N-ends of each monomer. This region is highly conserved and is responsible for about 75% of the dimer-stabilization energy. This report describes the latest lipopeptides and molecular hairpins that inhibit dimerization. These new molecules all have decreased peptide characteristics due to the presence of peptidomimetic groups that have peptide-like hydrogen bonding properties. Remarkably, they act *in vitro* against mutated proteases similar to those found in AIDS patients. The mechanism of inhibition was established using a combination of kinetic and biophysical methods (ultracentrifugation).