Supplementary Material

Conformational flexibility in the flap domains of ligand free HIV protease

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Supplemental Figure legends

Figure S1a. Flap conformational changes induced by TL-3 binding to 6X HIV protease in the 'flipped' conformation.

In the absence of any substrate or inhibitor, the flap regions of apo 6X HIV protease adopt an expanded 'open' conformation (tan) in which the flaps are in a 'top-to-top' relationship, but too far apart to form stabilizing interactions. The conformation of the flaps in the TL-3 complex (light-blue), and that adopted by the inhibitor (which contains a C2 axis), is distinctly asymmetric. In the 'flipped' half of the TL-3 complex, the flap is more distal from the active site, but the P4 benzyl group undergoes major rearrangement. Relative to apo 6X PR, TL-3 binding causes the flap to shift 6.3 Å. The 80s loop also shifts toward the inhibitor by 3.5 Å, allowing interaction of Pro81' and the P1 benzyl group.

Figure S1b. Flap conformational changes induced by TL-3 binding to 6X HIV protease in the 'non-flipped' conformation.

In this figure, the PR dimer is rotated 180^{o} relative to Fig. S1a to facilitate comparison of the 'flipped' and 'non-flipped' conformations. When compared to apo 6X PR in the expanded 'curled' conformation (tan), the flap shifts 8.3 Å in the 'non-flipped' half of the dimer, but the P4 benzyl group is not rearranged and no contact is formed between Pro81 and the P1 benzyl group.

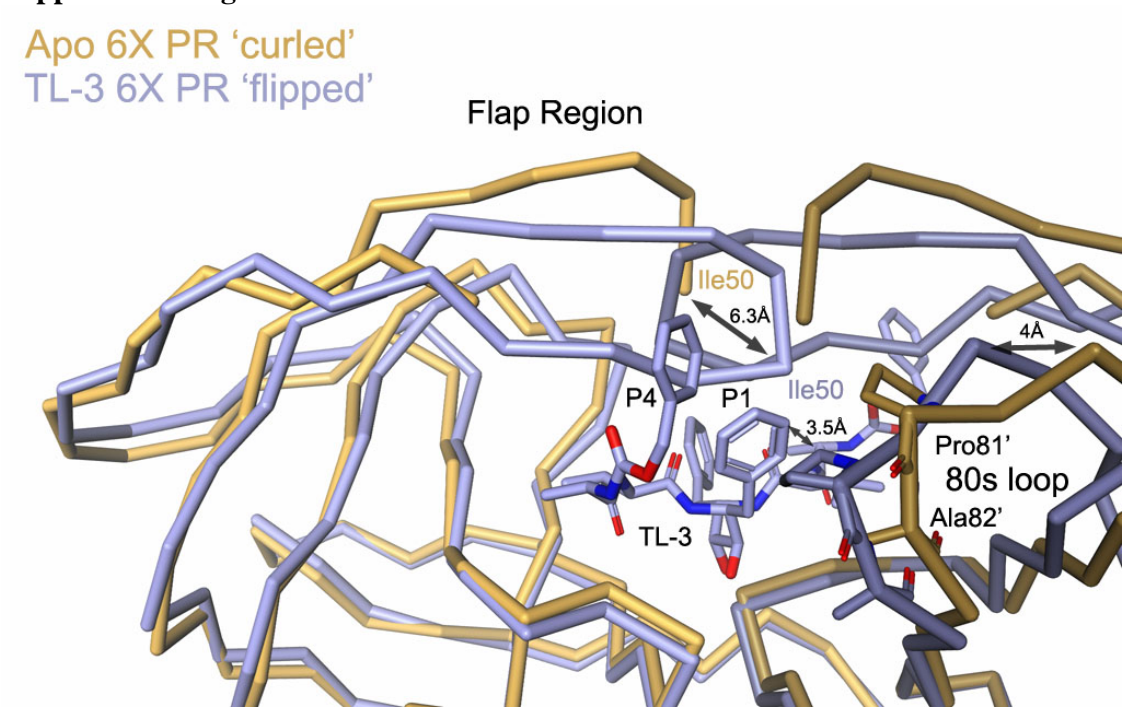
Figure S2a. Crystal packing contacts formed by the 'open' group of apo wild-type HIV proteases.

Crystal packing interactions formed in the tetragonal lattice of the apo PR structures that exhibit the 'open' conformation. The lattice positions of crystallographically related molecules are the same for both groups, but the specific contacts depend upon the flap conformations. When in the 'open' conformation (rose), the flap on one subunit of the dimer forms crystal packing contacts with residues 39', 41', and 61' of a 2-fold related dimer (grey), and vice versa (aqua blue).

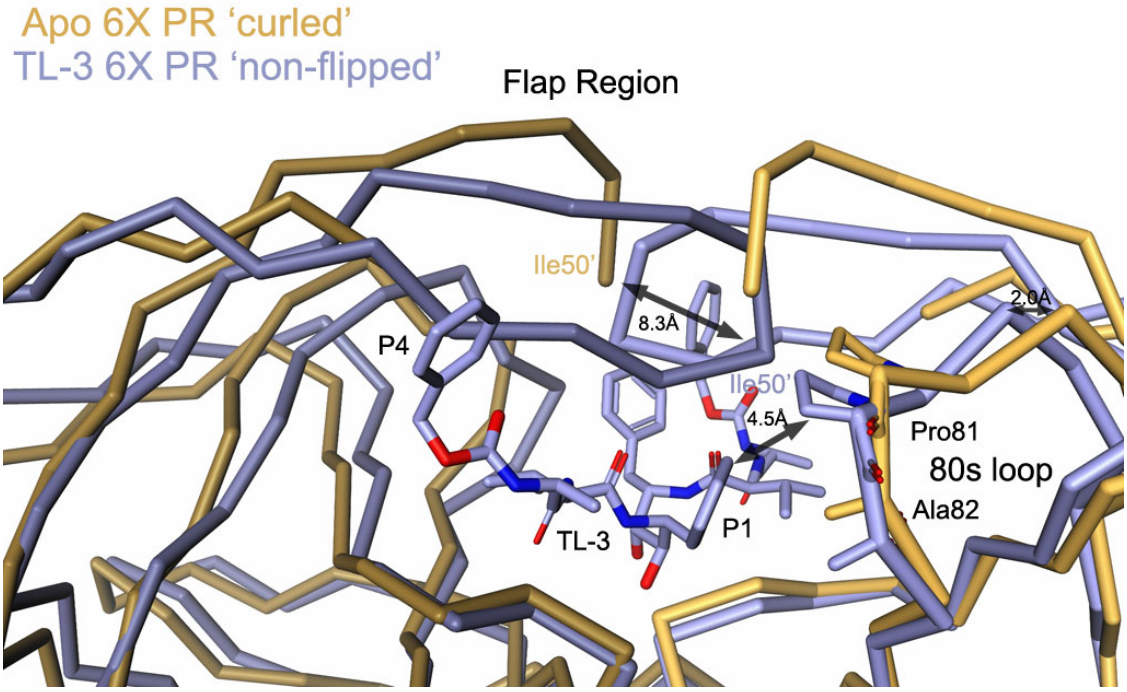
Figure S2b. Crystal packing contacts formed by the 'curled' group of apo wild-type HIV proteases.

Crystal packing interactions formed in the tetragonal lattice of the apo PR structures that exhibit the 'curled' conformation. When in the 'curled' conformation (green), the flap on one subunit of the dimer forms crystal packing contacts with residues 61', 72', and 92' of a 2-fold related dimer (grey), and vice versa (aqua blue).

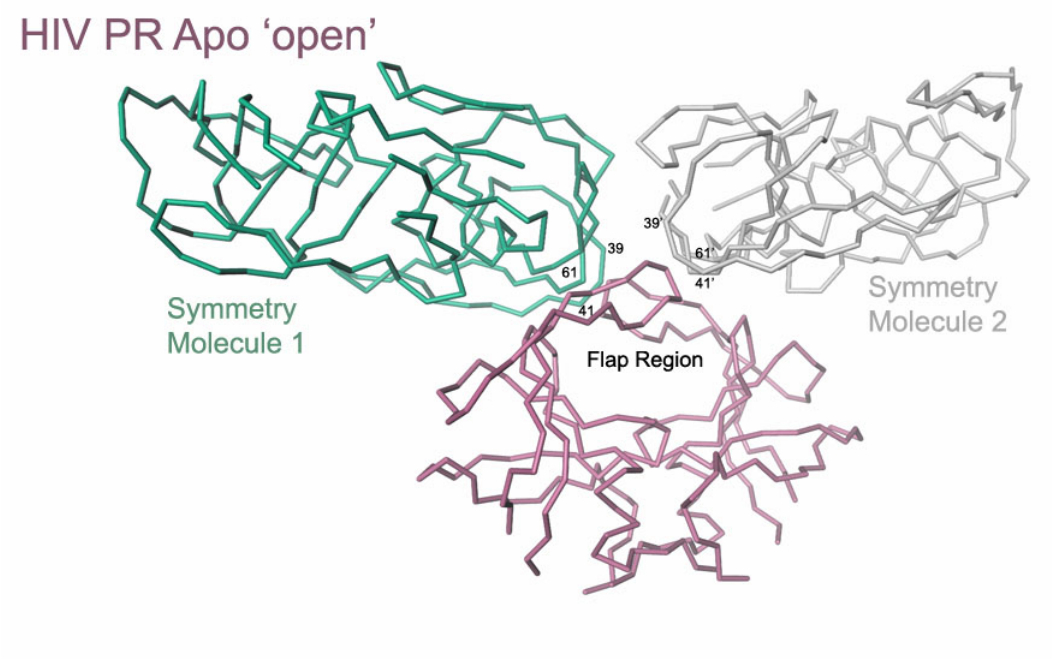
Supplemental Figure S1a



Supplemental Figure S1b



Supplemental Figure S2a



Supplemental Figure S2b