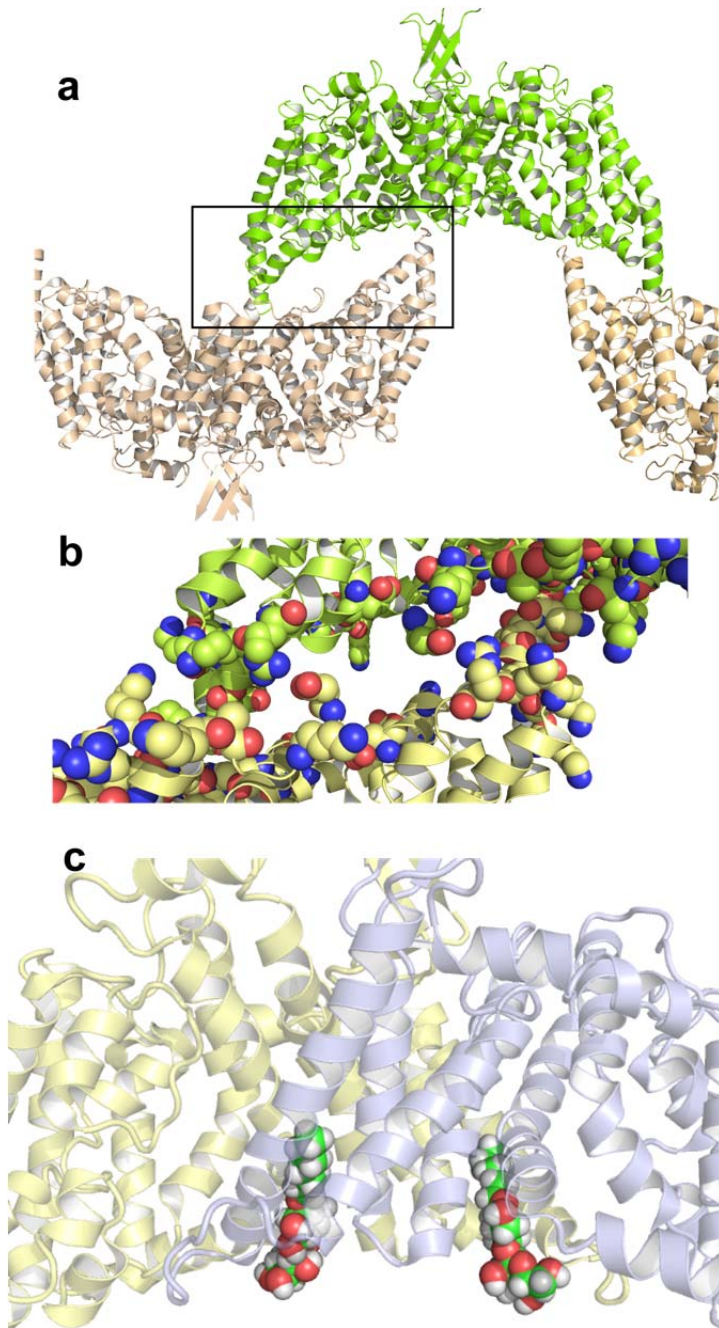
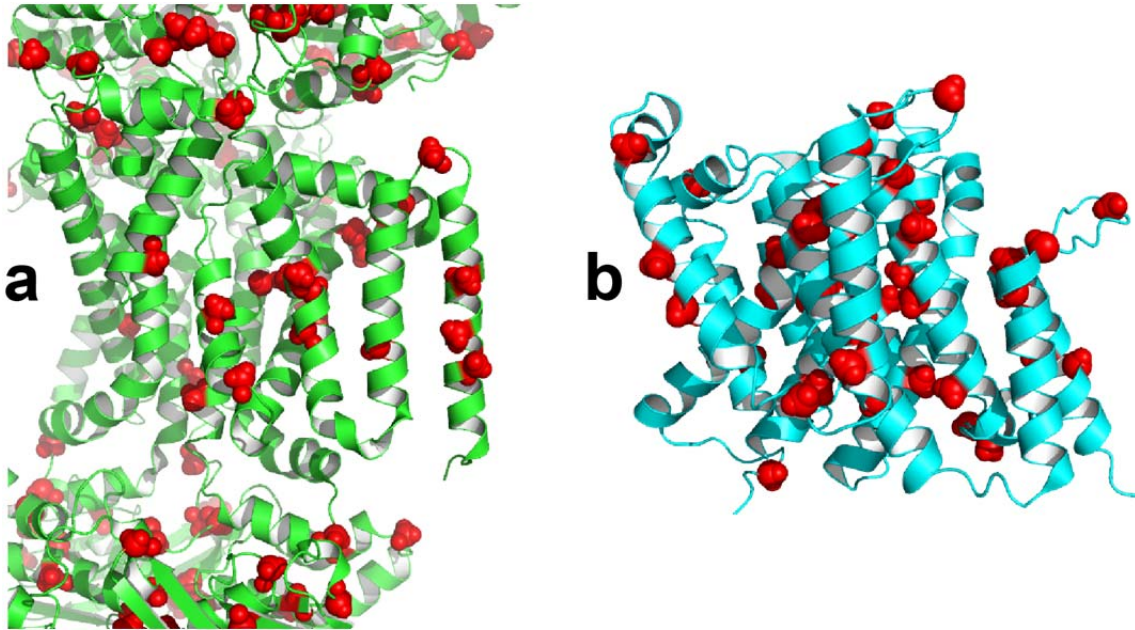


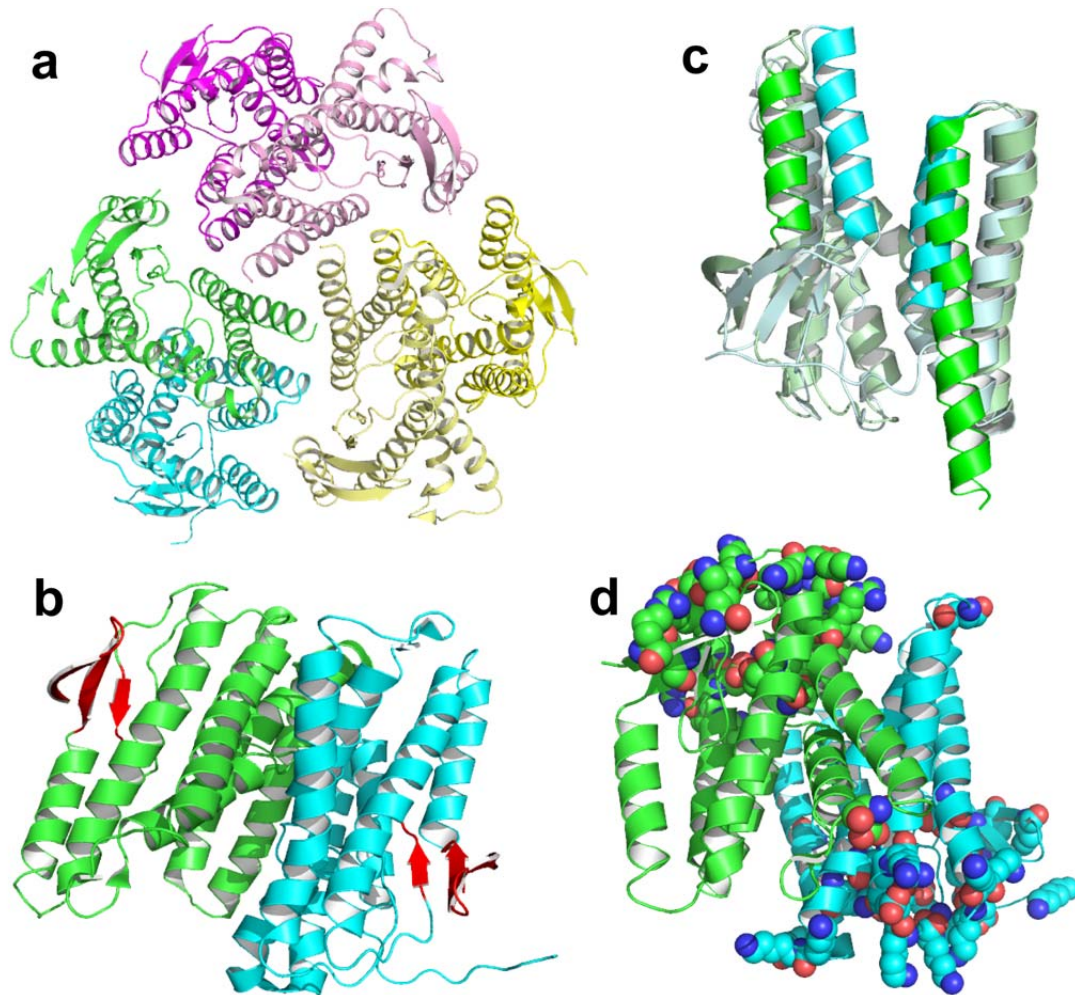
**Supplemental Figure 1.** Aromatic residues shielding the backbone of an amphipathic loop in the rhomboid protease (2IC8). (a) Backbone amide and carbonyl groups highlighted. (b) Aromatic side chains that shield the backbone polar sites from the hydrophobic environment.



**Supplemental Figure 2.** Crystal contacts and detergent molecules in the saccharide transporter ChbC (3QNQ). (a) Highly curved cytosol-facing surface, in part due to apparently displaced TM8 and TM10 helices, which form crystal contacts (*boxed region*). (b) Enlarged view of the boxed region in panel a, highlighting charged residues. (c) Two detergent molecules inserted at the dimer interface.



**Supplemental Figure 3.** Examples of poor packing of helices with the rest of the transmembrane (TM) domain. (a) MalF subunit of the maltose transporter complex (3RLF), with the first two TM helices apparently separated from the rest of the protein. (b) NCS2 transporter (3QE7), with the last two TM helices apparently terminated prematurely, positioning the intrahelical loop in the would-be hydrophobic environment. In both panels *a* and *b*, Gly residues are displayed in red.



**Supplemental Figure 4.** Possible nonnative-like features in the structure of the site-2 protease (3B4R). (a) Trimer of dimers arrangement in the crystal lattice. Two antiparallel, asymmetric monomers (molecules A and B, respectively) comprising a dimer are displayed in green and cyan. Note the three-helix bundle formed around the three-fold symmetry of the trimer. Additional crystal contacts occur between helix 1 of molecule A and a neighboring molecule B. (b)  $\beta$ -sheet cap (red) of the first helix. (c) Superposition of molecules A and B, showing that helices 1 and 6 (green) in molecule A have much wider opening than their counterparts (cyan) in molecule B. (d) Misalignment between the bilayer-like crystal lattice and the interfacial plane defined by the charged residues. In the view shown, the threefold symmetry axis of the trimer (representing the orientation of the crystal lattice) is directed vertically; the interfacial plane is slanted so that the charged residues appear to spread over most of the hydrophobic thickness of the monomers.