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Supporting information for article:

X-ray structure of alisporivir in complex with cyclophilin A at 1.5 Å resolution

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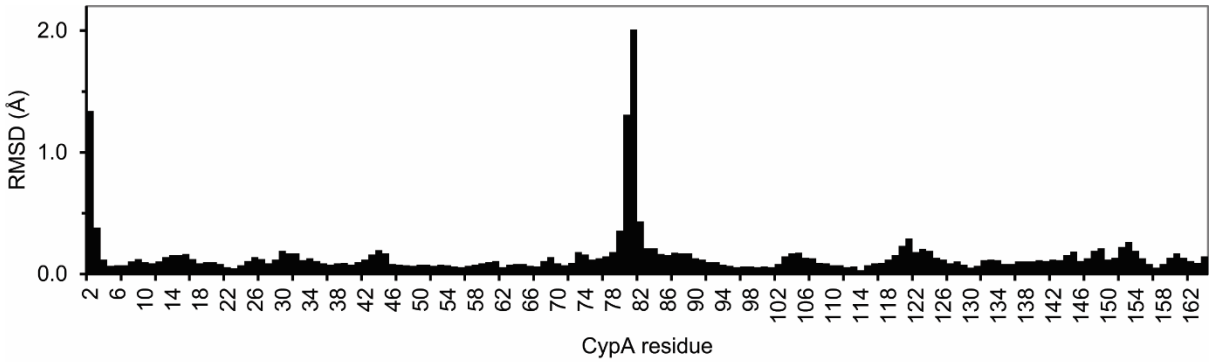
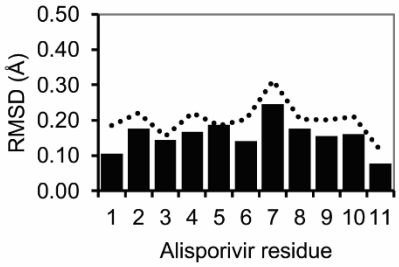


(*a*)



(*b*)

Figure S1 Model deviations among the four CypA-Alisporivir complexes in the asymmetric unit. (*a*) The four CypA strucures (chains A, B, C, D) have been superposed using the backbone atoms (N, Cα, C) of residues 2 to 164 and a per residue backbone RMSD value (Å) has been calculated using the average3d.py script from C. Mura (http://muralab.org). Residue-specific RMSDs for each backbone atom (N, Cα, C) have been calculated as an average over all unique pairs within the bundle (chains A, B, C, D), then they were averaged to keep one value per residue. (*b*) The least square fitting of the four Alisporivir structures (chains E, F, G, H) has been performed using all atoms, then per residue all atoms (dotted line) and backbone (black bars) RMSD values (Å) have been calculated among them. Residue-specific RMSDs have been calculated as described in (*a*).

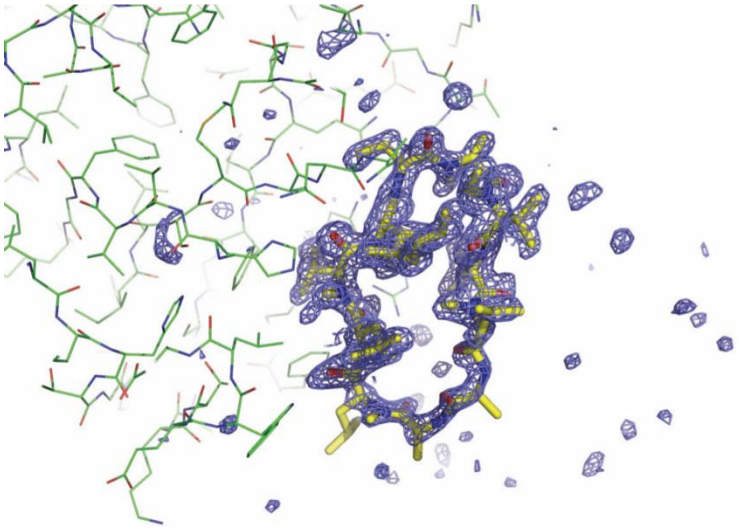


Figure S2 The mFo-DFc omit map of the CypA-ALV structure, refined without the ligand, contoured at 2.5 σ and displayed as a blue mesh. CypA and ALV are coloured in green and yellow, respectively.

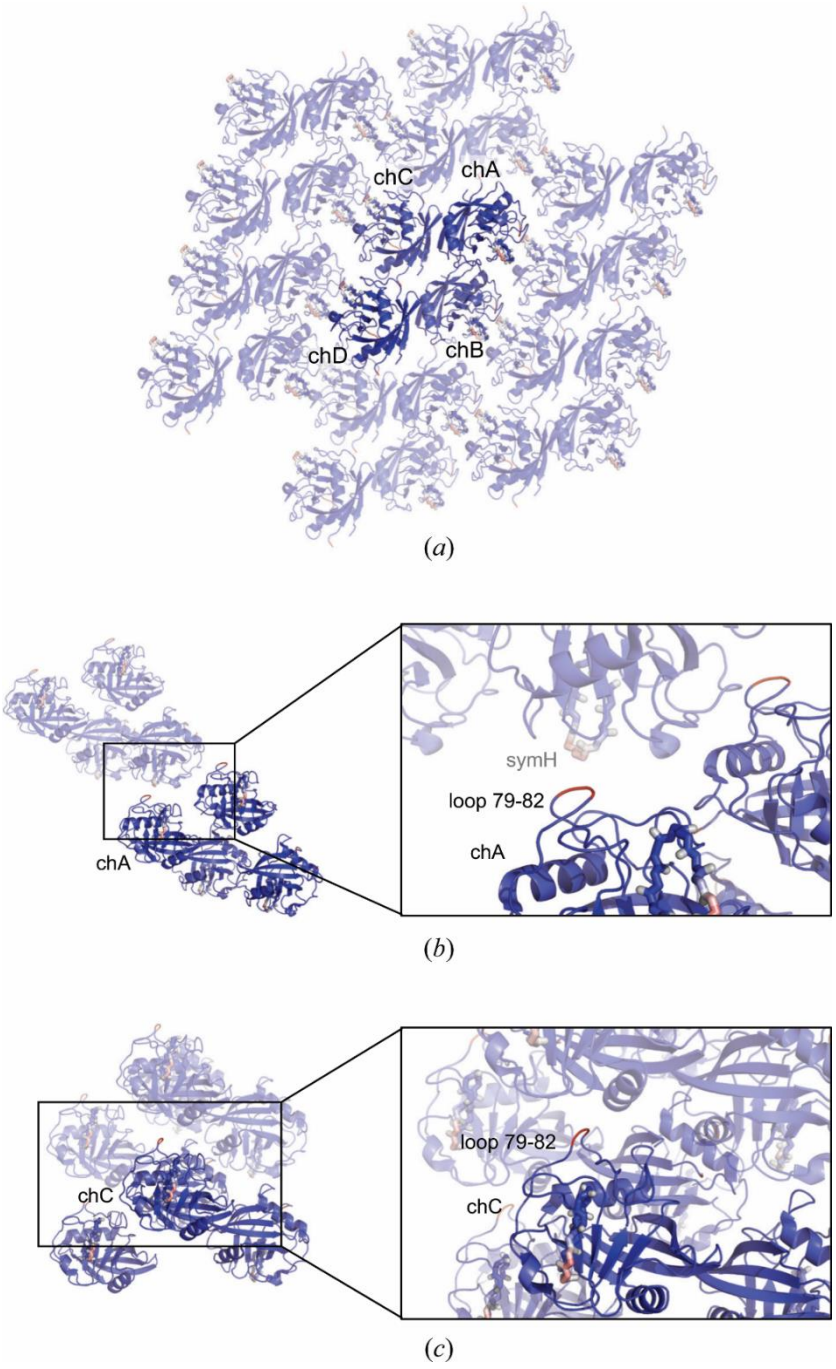
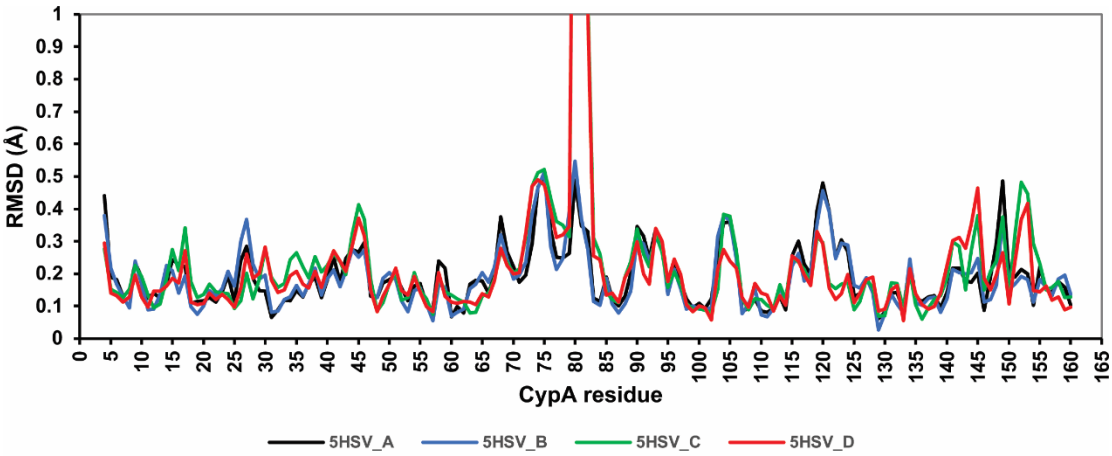
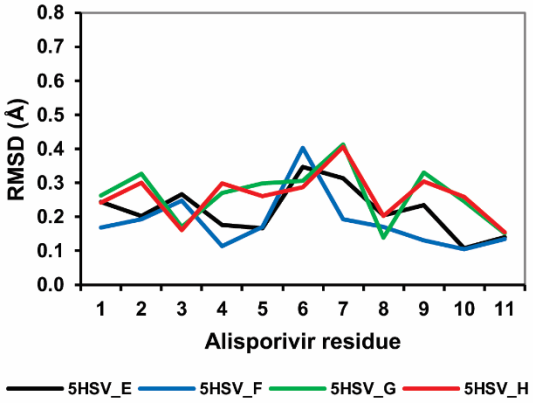


Figure S3 Crystal packing and model deviations. Four CypA-Alisporivir complexes (chA-chE, chB-chF, chC-chG and chD-chH) are contained in the asymmetric unit. The structures of CypA and Alisporivir are coloured based on their per residue backbone RMSD values (see Figure 3). (*a*) The molecules present in one asymmetric unit are highlighted in thicker ribbon. (*b*) Crystal contacts between the loop 79-82 in CypA from chain A (chA) and a symmetry-related Alisporivir molecule (symH). A similar steric hindrance is observed for CypA from chain B (chB) and a symmetry-related Alisporivir molecule (symG) (data not shown). (*c*) The loop 79-82 in CypA from chain C (chC) or chain D (chD) is not constrained by crystal packing.



(*a*)



(*b*)

Figure S4 Comparison of the CypA-Alisporivir and CypA-CsA complexes. Average per-residue backbone RMSD (Å) (*a*) between each CypA structure when bound to Alisporivir (PDB ID: 5hsv, chA-D) with CsA-bound CypA (PDB ID: 1cwa, chA) and (*b*) between each CypA-bound Alisporivir molecules (PDB ID: 5hsv, chE-H) and CypA-bound CsA (PDB ID: 1cwa, chC). The per-residue specific RMSDs were calculated using the PyMOL RmsdByResidue.py script (https://pymolwiki.org).

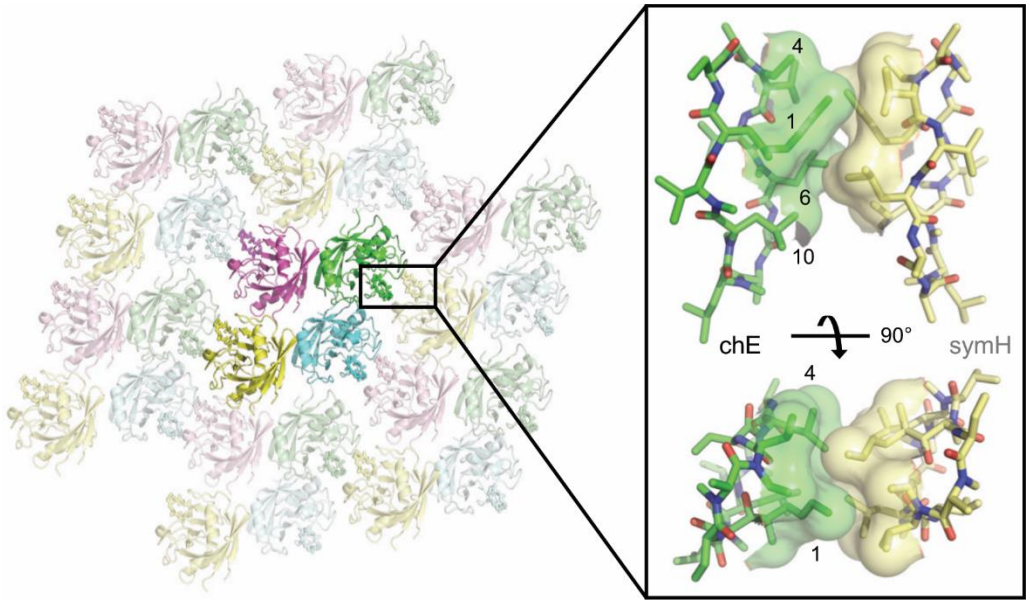


Figure S5 Crystal packing of the CypA-Alisporivir complex. Four CypA-Alisporivir complexes (chA-chE, chB-chF, chC-chG and chD-chH) are contained in the asymmetric unit. They are shown in green, cyan, magenta and yellow respectively (as in Figure 2a). The molecules in one asymmetric unit are highlighted in thicker ribbon. Inset shows a zoomed in view of the intermolecular contacts between Alisporivir (chE, in green) and another symmetry-related ligand molecule (symH, in pale yellow). Of note, similar contacts are observed for the other chains of ALV (chF with symG, chG with symH and chH with symE). The molecular surfaces corresponding to the Alisporivir atoms engaged in the crystal contacts are shown. Figure was generated using PyMOL (Molecular Graphics System, Version 1.8 Schrödinger, LLC).