X-ray crystal structure analysis of a multidrug-resistant variant of HIV-1 protease in complex with a chroman-4-amine containing protease inhibitor.

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This communication describes the X-ray crystal structure of a multidrug-resistant variant (MDRv) of Human immuno--deficiency virus type-1 (HIV-1) protease (1) in complex with a chroman-4-amine containing inhibitor (C4A). Previously, the X-ray crystal structure of this MDRv HIV-1 protease was solved in complex with other inhibitors (2). The current structure (PDB ID: 4RVX) was solved in the $P2_1$ space group with two protease dimers per asymmetric unit with each dimer bound to a single molecule of C4A. The overall root mean square deviation (RMSD) of C_α atoms from both protease dimers within the asymmetric unit was less than 1 Å and was considered insignificant. The overall dimer protease structure looks similar to that of a typical wild type HIV-1 protease bound to an inhibitor with the two flaps closed onto the inhibitor (Figure 1).

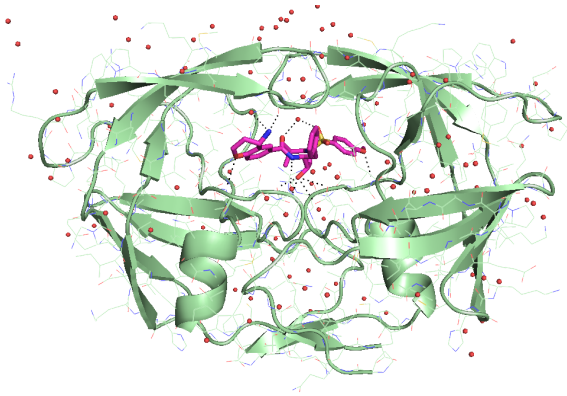

Figure 1. X-ray crystal structure of MDRv HIV-1 protease (pale green color) in complex with an inhibitor, C4A (magenta color).

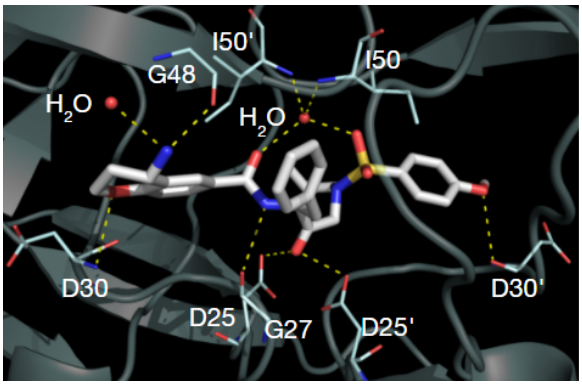

Figure 2. C4A (white color) is bound in the active site of MDRv HIV-1 protease (grey color) with multiple polar contacts (shown as yellow dashed lines) along with water molecules (red spheres).

In this report, the C4A is bound in the active site of the MDRv HIV-1 protease with 9 hydrogen bonds of which 3 are with conserved crystallographic water molecules (Figure 2). Contiguous electron density was seen for C4A at a contour of 2.5 σ in the active site of the MDRv HIV-1 protease (Figure 3). The oxygen and nitrogen atoms from the chroman-4-amine moiety bound in the S2-binding pocket of the MDRv HIV-1 protease exhibit one hydrogen bond (polar contact) each with D30 and G48, respectively. The nitrogen atom from chroman-4-amine moiety is also involved in direct hydrogen bonding with a conserved water molecule. The oxygen atom from the transition state-mimic hydroxyl group shows one hydrogen bond each with the side chain carboxyl groups of D25 and D25'. The oxygen atom from the P2'-benzene methoxy group shows one hydrogen bond with D30'.

Additionally, one hydrogen bond was seen with G27. The average bond length of these hydrogen bonds was calculated to be around 2.5 Å, indicating strong interactions with the MDRv HIV-1 protease. The C4A also has multiple hydrophobic interactions with the MDRv HIV-1 protease. The amino acids involved in these hydrophobic interactions include A28, D29, D30 and I50' in the S2-binding pocket; G49, P81', T82' and I84' in the S1-binding pocket; I84 and G27' in S1'-binding pocket; I50, A28', D29' and V32' in the S2'-binding pocket.

With a good binding profile, the C4A appears to be bound in the active site of the MDRv HIV-1 protease with reasonable binding affinity. However, owing to the flexibility in the overall structure of HIV-1 protease in general (3, 4) and MDRv in specific (5), the binding affinity of C4A may or may not be in par with the existing protease inhibitors such as darunavir that are currently in clinical use. In other words, molecular dynamics simulations (data not shown here) revealed the flap opening in spite of the presence of an inhibitor bound in the active site in the case of MDRv HIV-1 protease. Due to this phenomenon, the chroman-4-amine moiety which is attached to the rest of C4A through a rotatable single bond changed its orientation resulting in complete loss of polar contacts in the S2-binding pocket of MDRv HIV-1 protease. This suggests that the chroman-4-amine has to bind in the S2-binding pocket in a certain binding orientation failing which would lead to loss of its binding affinity. Although the biochemical assays indicated good binding affinity of C4A to wild type HIV-1 protease (data will be published elsewhere), the same cannot be translated to the MDRv HIV-1 protease especially in cell-based assays owing to the cell penetration capability of C4A (6) and in-cell antiviral potency.

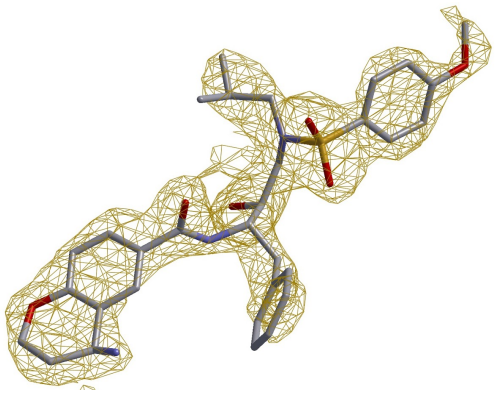

Figure 3. The difference electron density map for C4A bound in the active site of MDRv HIV-1 protease. This map is contoured at 2.5 σ.

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