Binding profile of VX-478 in the active site of a multidrug-resistant HIV-1 protease, an X-ray crystal structure analysis

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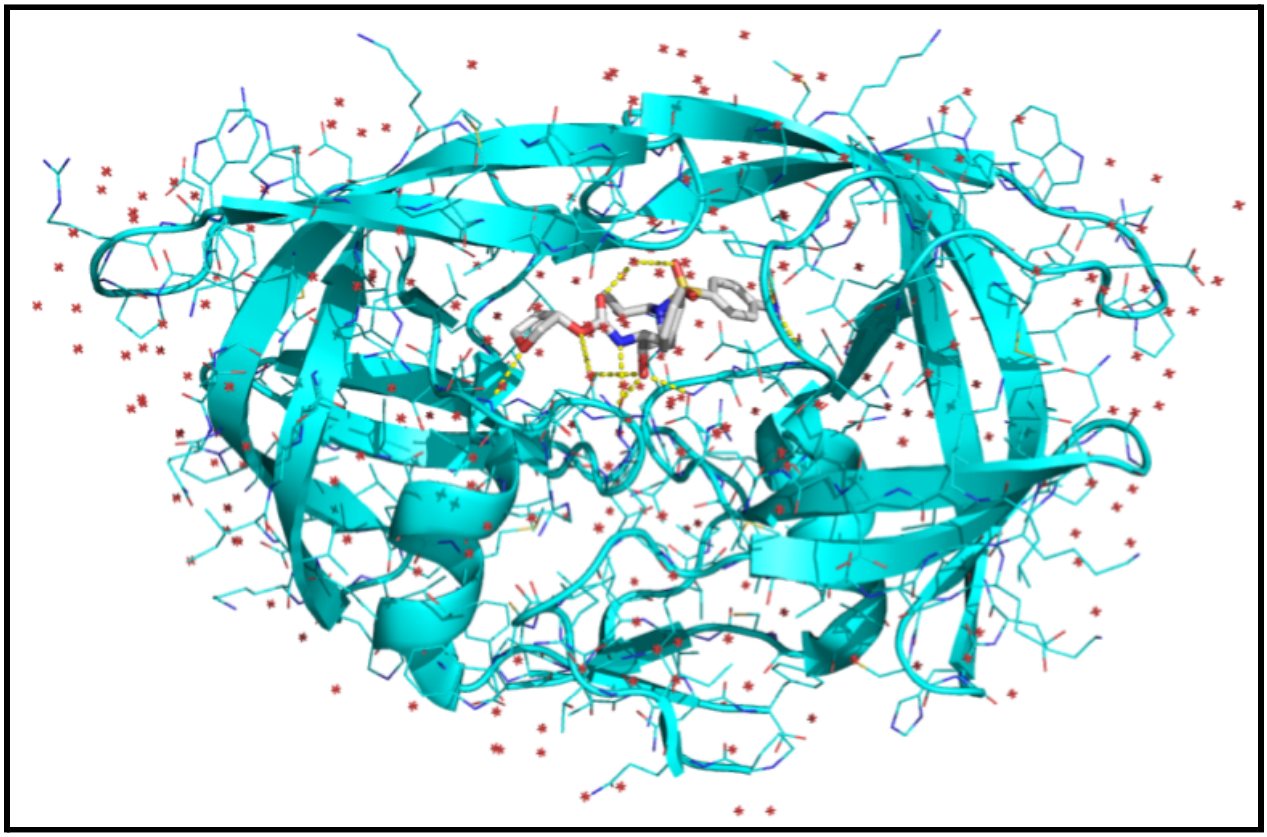

Figure 1. X-ray crystal structure of MDRv HIV-1 protease (cyan color) in complex with VX-478 (white color) and the surrounding water molecules (red stars).

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 amprenavir (VX-478). 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: 4RVJ) was solved in the $P2_1$ space group with two protease dimers per asymmetric unit with each dimer bound to a single molecule of VX-478. 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.

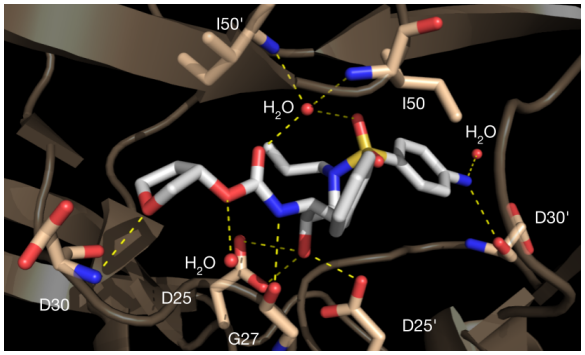

Figure 2. VX-478 (white color) is bound in the active site of MDRv HIV-1 protease (beige color) with multiple polar contacts (shown as yellow dashed lines) along with water molecules (red spheres).

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). In this report, the VX-478 is bound in the active site of the MDRv HIV-1 protease with 10 hydrogen bonds of which 4 are with conserved crystallographic water molecules (Figure 2). Contiguous electron density was seen for VX-478 at a contour of 2.5 σ in the active site of the MDRv HIV-1 protease (Figure 3). The P2 moiety of VX-478 contains mono-tetrahydrofuran (mono-THF) ring. The oxygen atom from this mono-THF ring shows one hydrogen bond with the backbone amide nitrogen atom of D30. Another oxygen atom that is outside of the ring within the P2 moiety shows a hydrogen bond with a conserved crystallographic water molecule within the active site of the MDRv HIV-1 protease. The amide nitrogen atom that joins the P2 and P1 moieties of VX-478 shows one hydrogen bond with the backbone carbonyl oxygen atom of G27. Both the catalytic aspartates, D25 and D25' show at least one hydrogen bond each with the transition state-mimic oxygen atom of VX-478. The P2' aniline group of VX-478 shows two hydrogen bonds, one with the backbone nitrogen atom of D30' and the other with a conserved crystallographic water molecule.

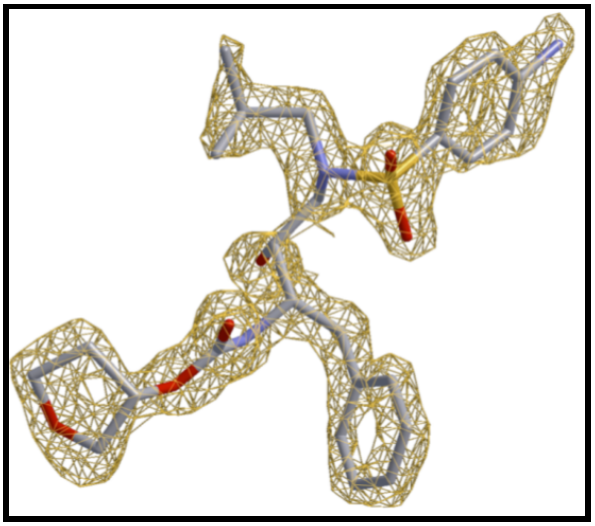

Figure 3. The difference electron density map for VX-478 bound in the active site of MDRv HIV-1 protease. This map is contoured at 2.5 σ.

Overall the VX-478 shows a similar binding profile to its own within the active site of the wild type HIV-1 protease. The only difference seen in this structure is that the P2 mono-THF moiety shows only one hydrogen bond instead of two (as seen in the wild type). This binding profile looks promising however, due to the multiple mutations in MDRv HIV-1 protease (3, 4), VX-478 may not control the protease dynamics (5) that may lead to loss of its potency as evident from the antiviral data (6).

References

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