Title: Quantum Mechanical Analysis of Newly Synthesized HIV-1 Protease Inhibitors: Evaluation of Wild-Type and Resistant Strain Binding Interactions

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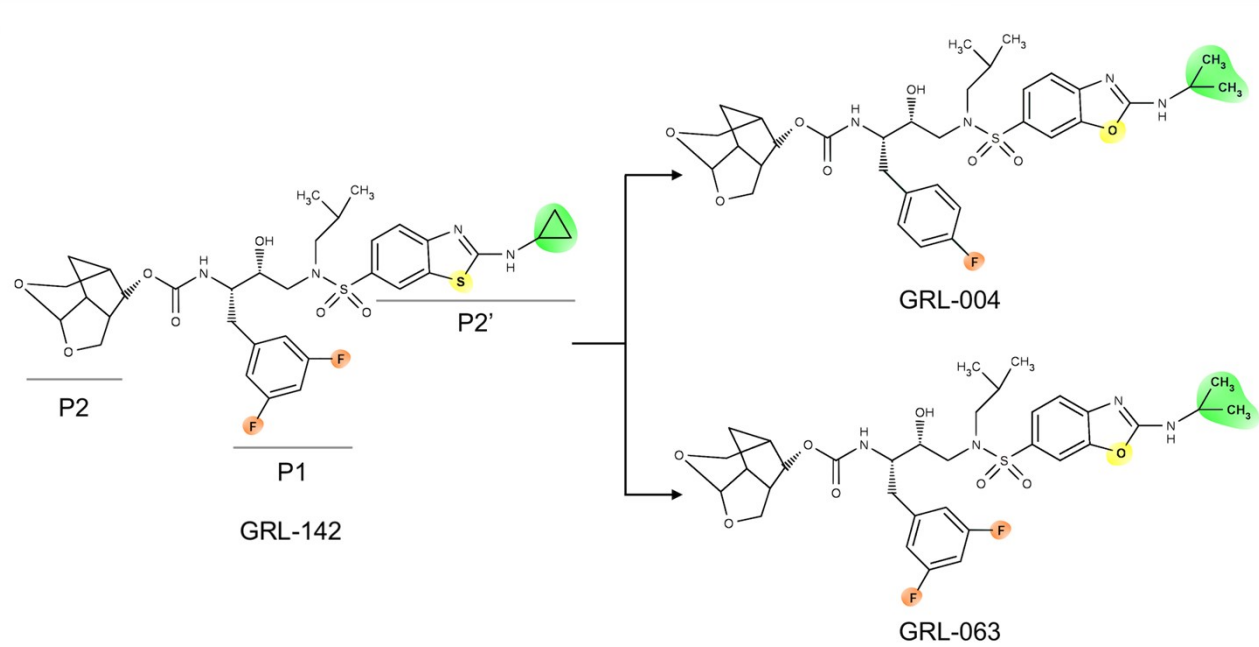
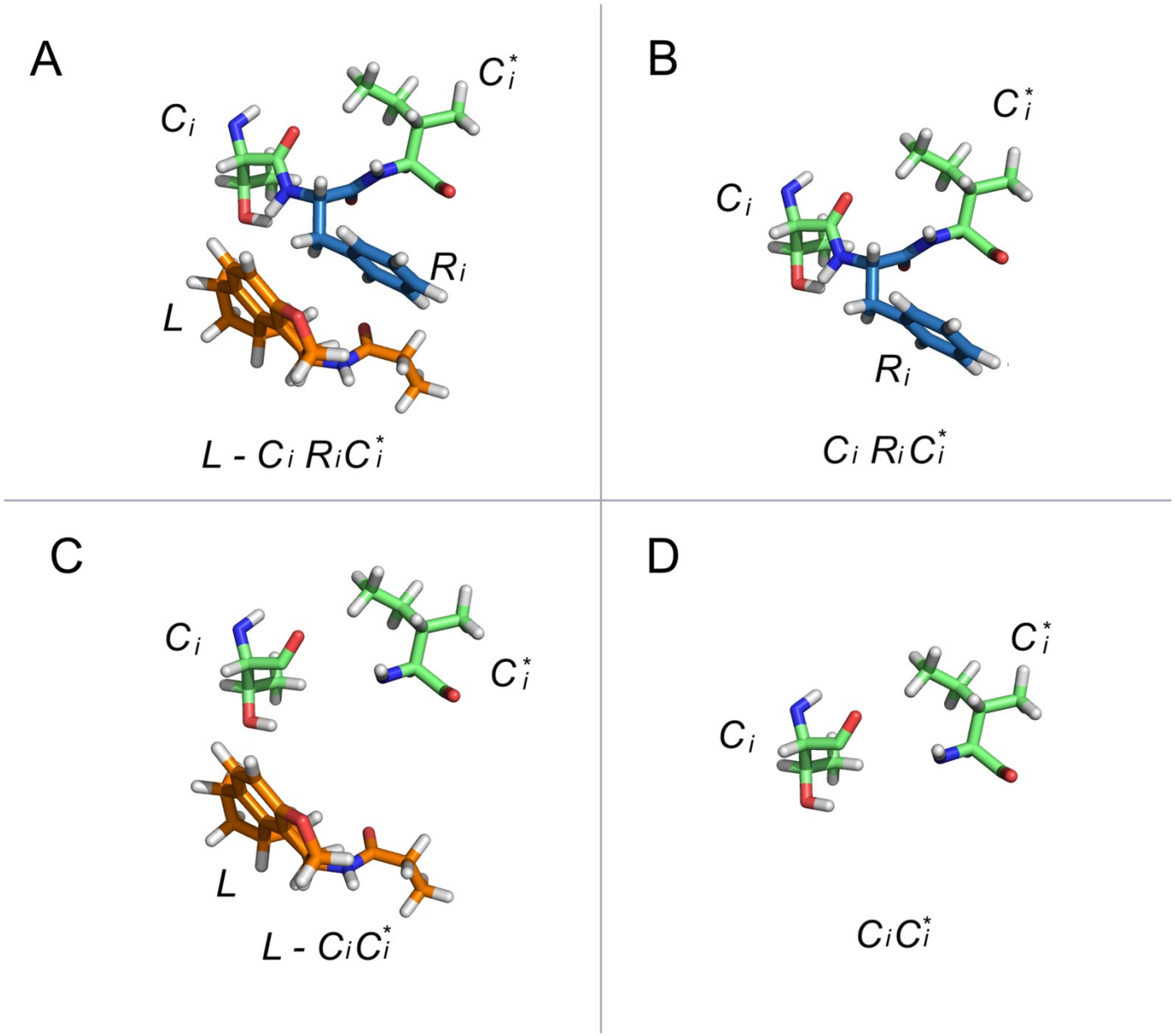
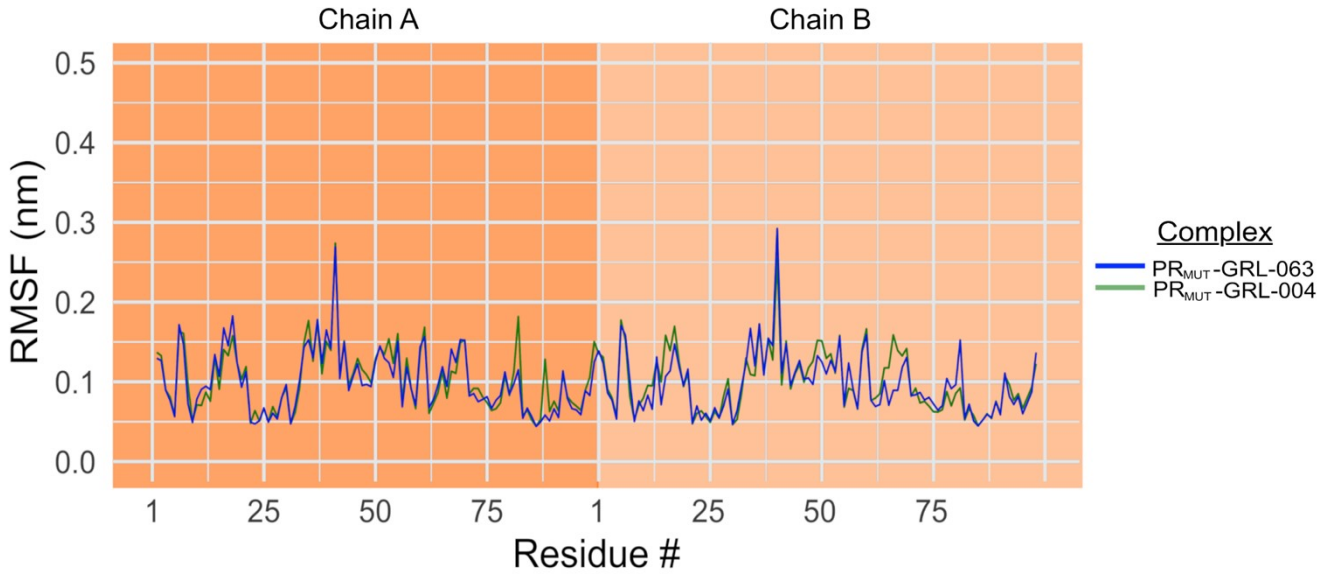
Supplementary Material



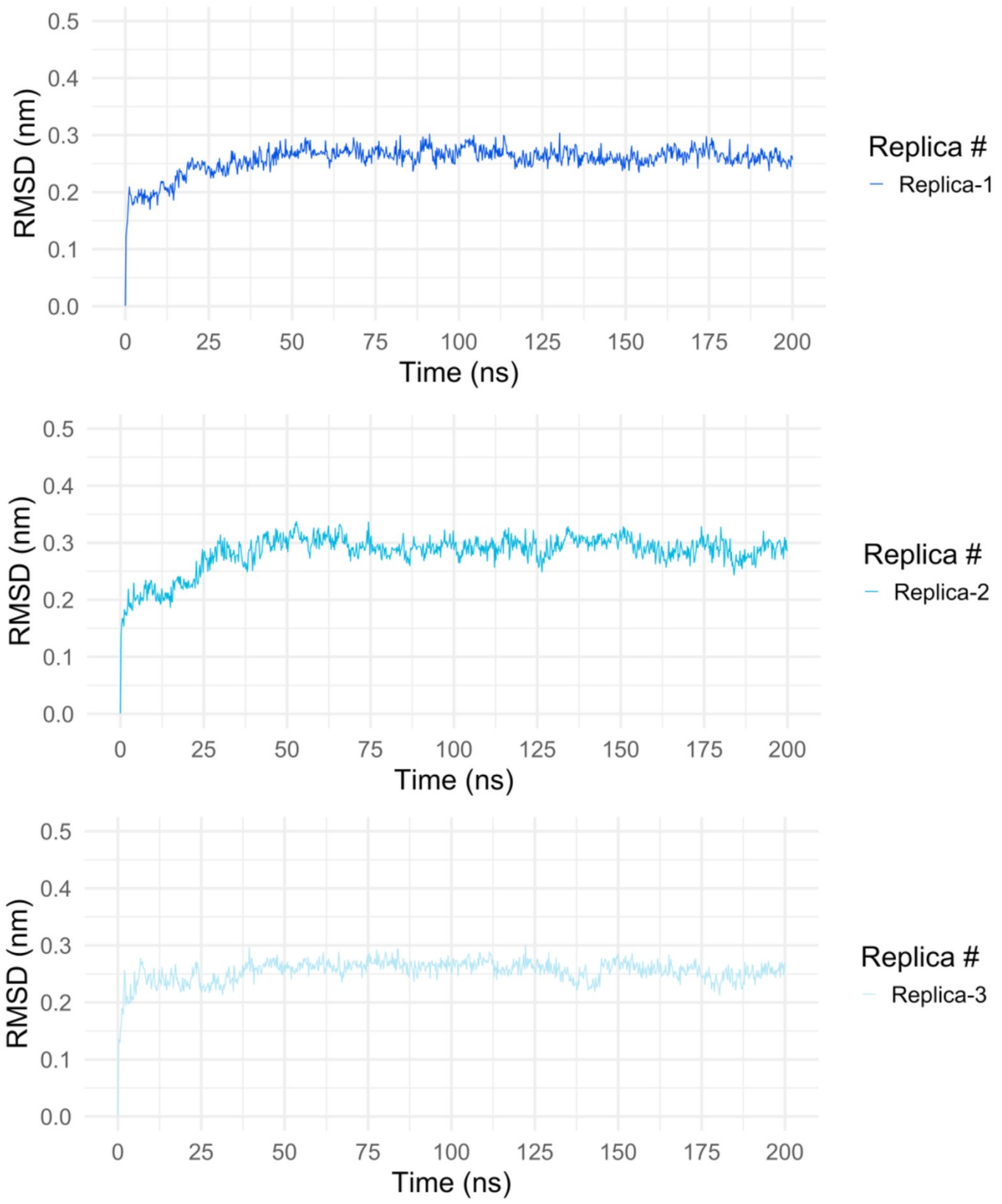
Supplementary Figure S1 - Structure of GRL-142 and the proposed modifications for the synthesis of molecules GRL-004 and GRL-063.



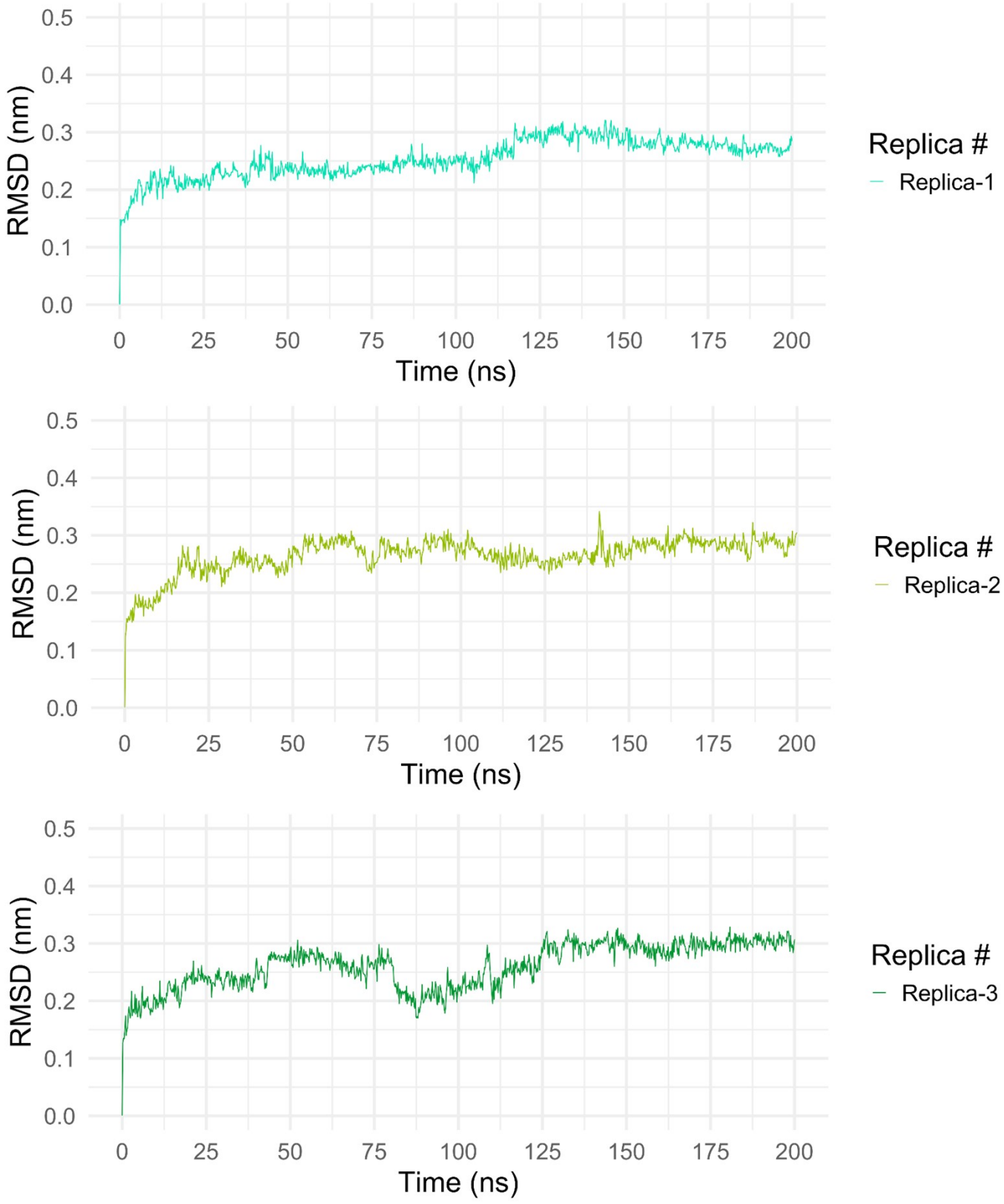
Supplementary Figure S2 - MFCC scheme showing the four terms of Equation 1. The ligand (L) is represented in orange stick, the main residue (Ri) is represented in blue stick and both caps (Ci and Ci*) are represented in green sticks.



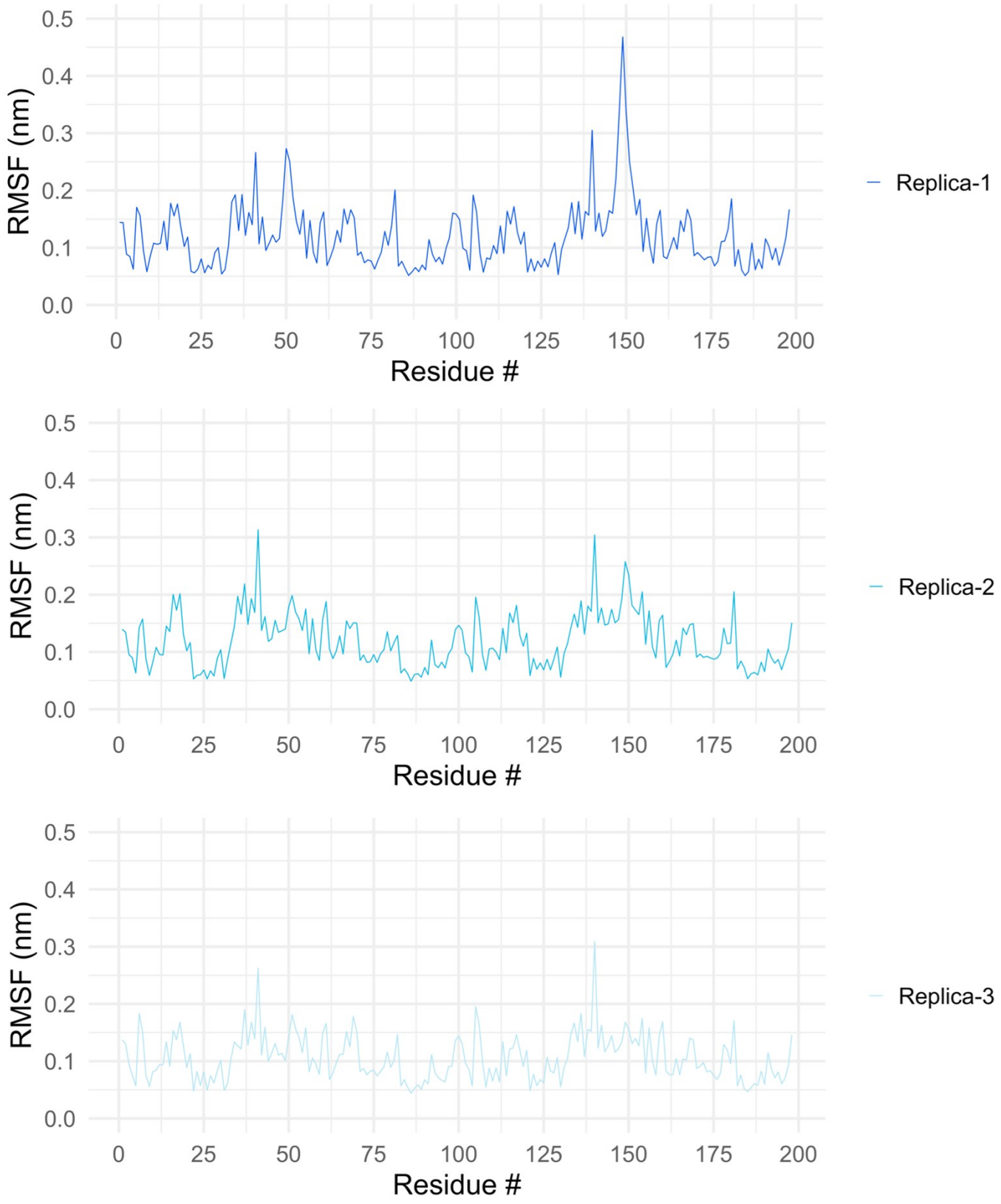
Supplementary Figure S3 - RMSF analysis between 150-200 ns of simulation



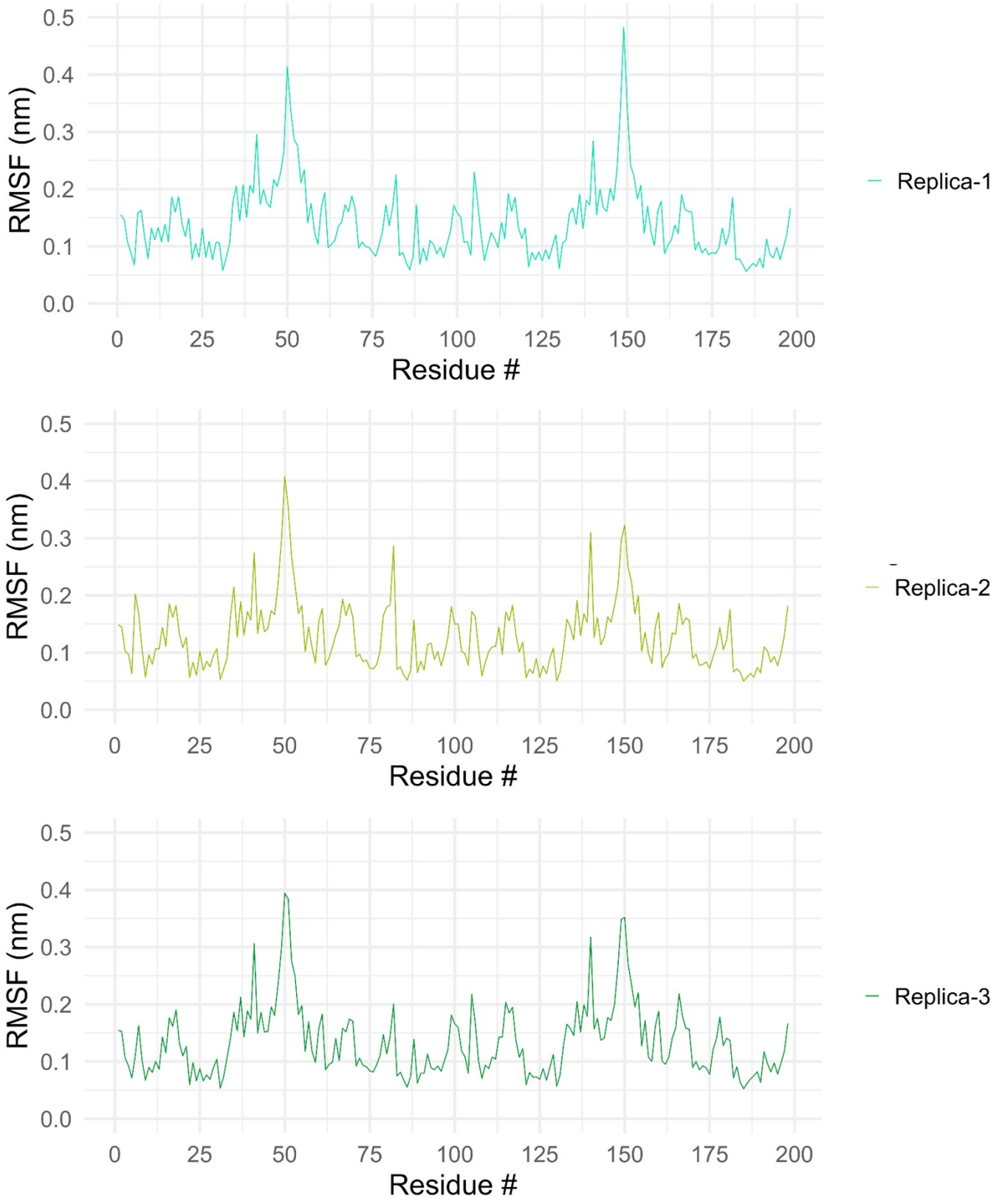
Supplementary Figure S4 - RMSD analysis of individual replicates of PR_{MUT}-GRL-063 complex



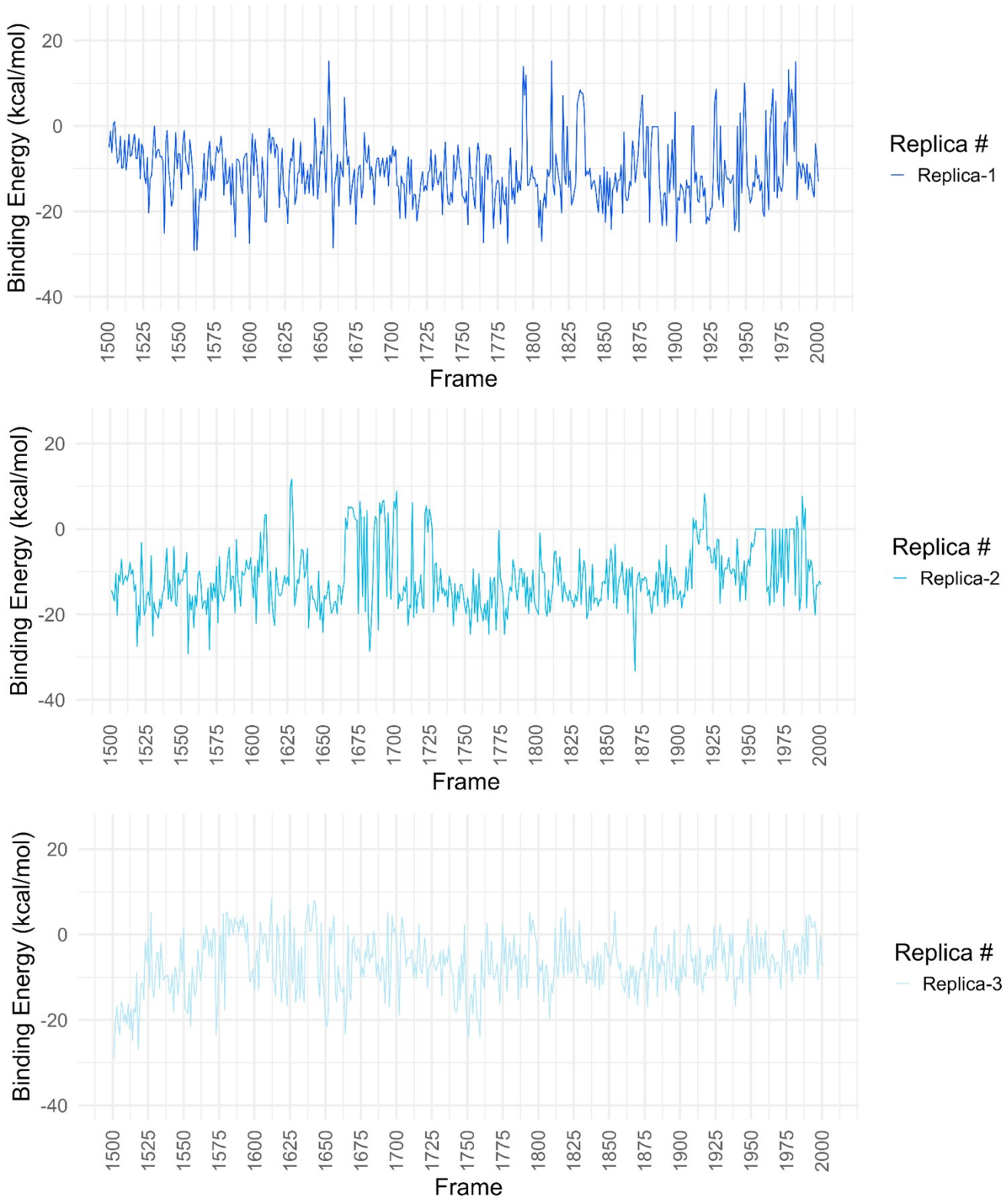
Supplementary Figure S5 - RMSD analysis of individual replicates of PR_{MUT}-GRL-004 complex



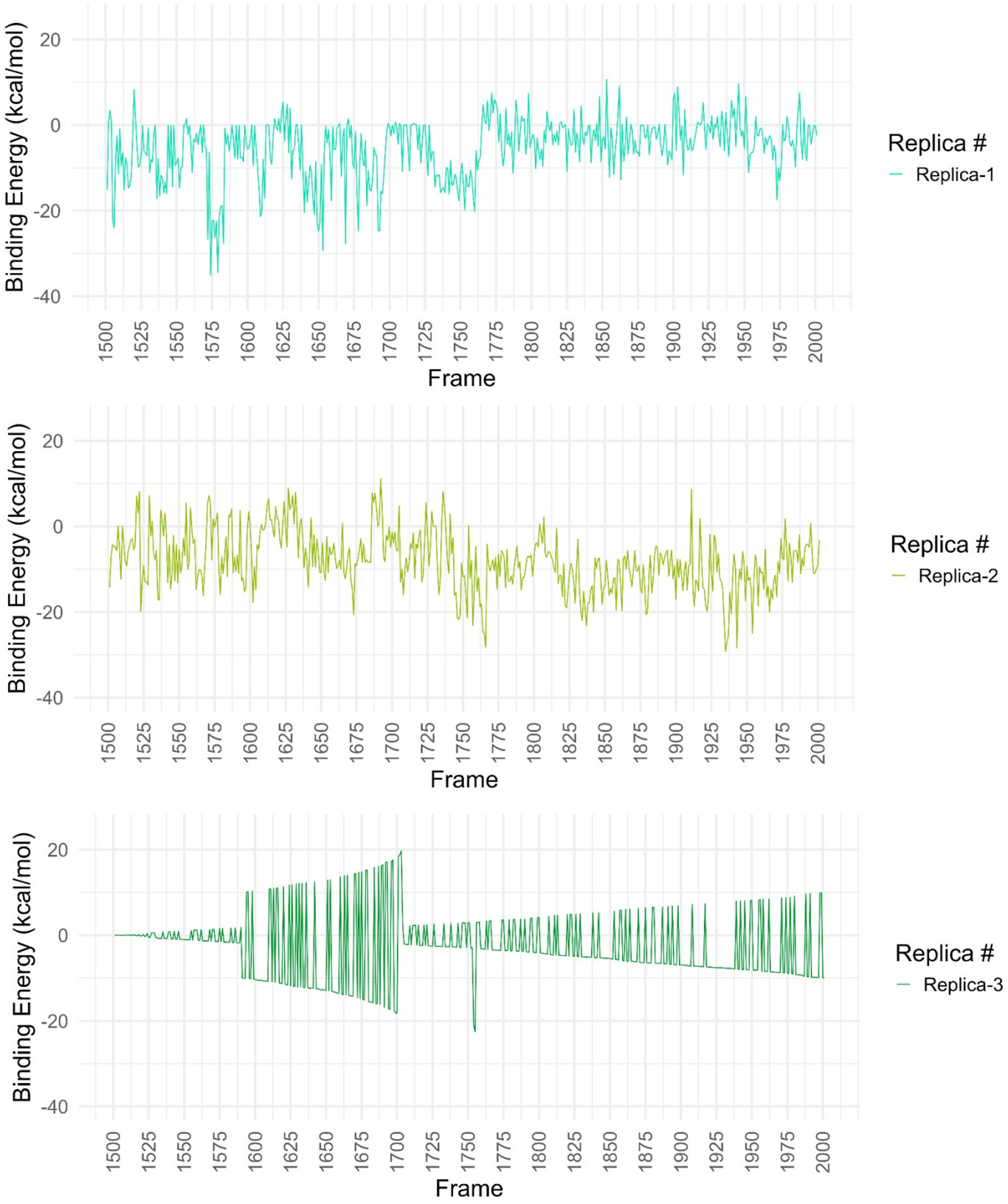
Supplementary Figure S6 - RMSF analysis of individual replicates of PR_{MUT}-GRL-063 complex



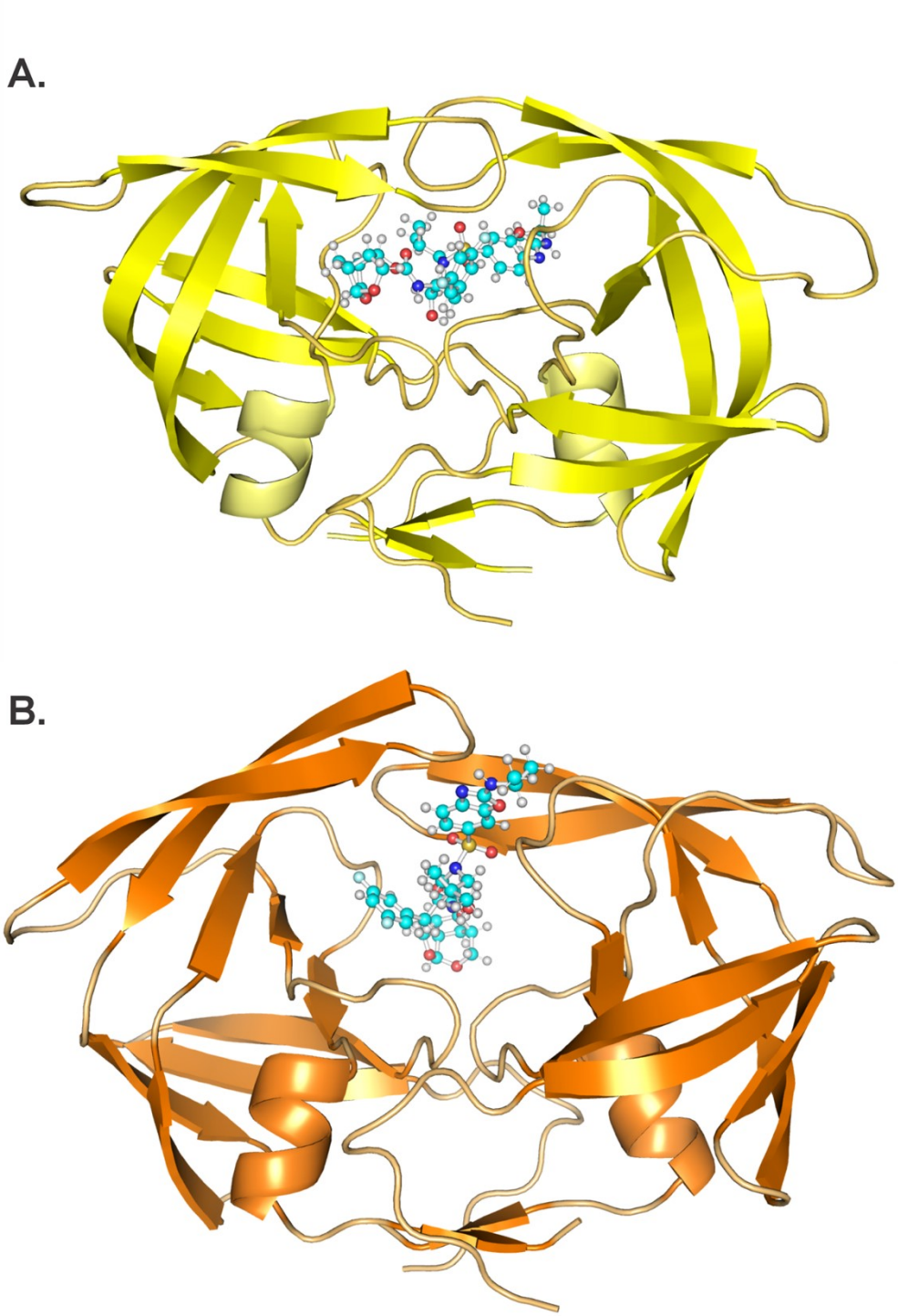
Supplementary Figure S7 - RMSF analysis of individual replicates of PR_{MUT}-GRL-004 complex



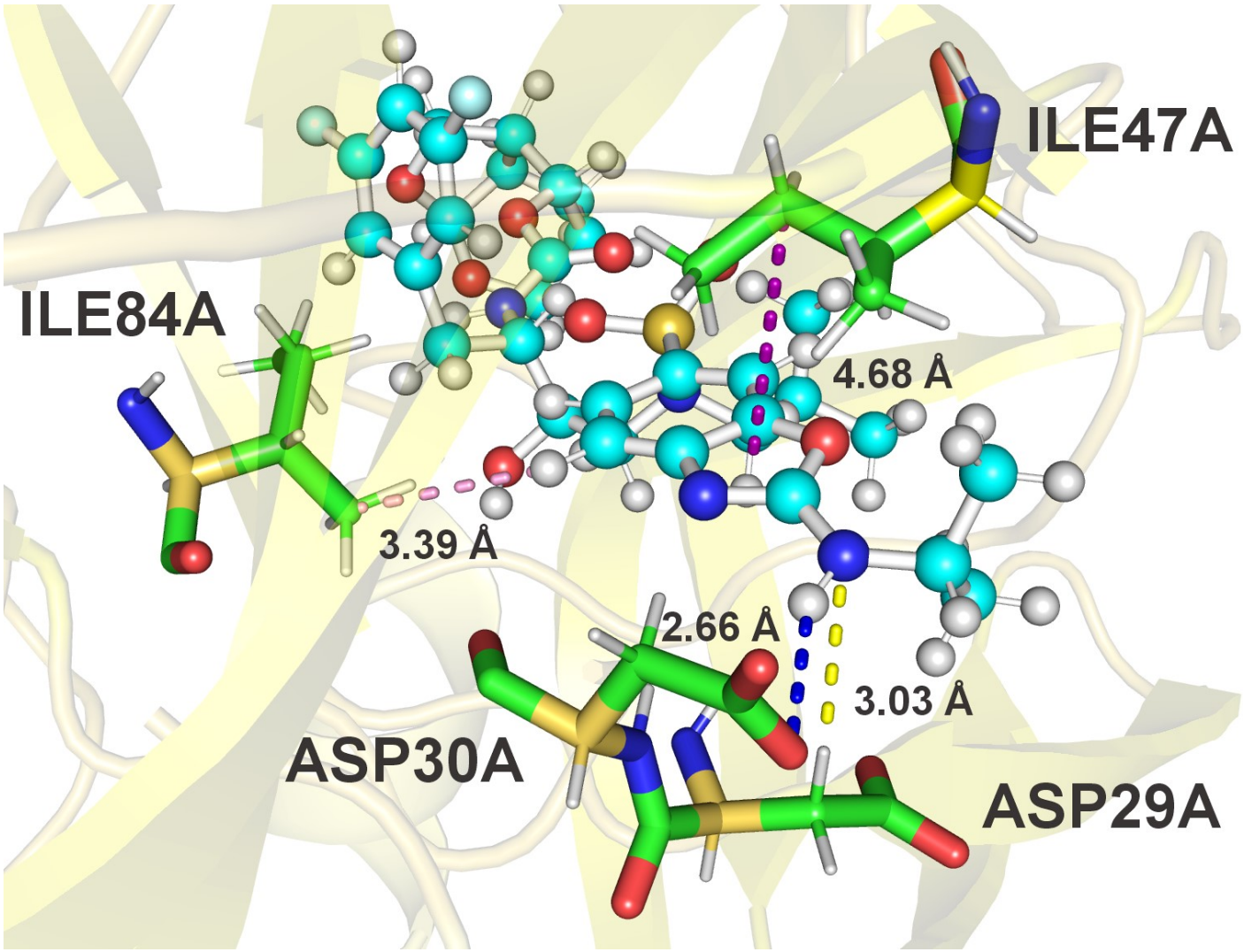
Supplementary Figure S8 - QM/MM analysis of individual replicates of PR_{MUT}-GRL-063 complex from the last 500 frames of trajectory



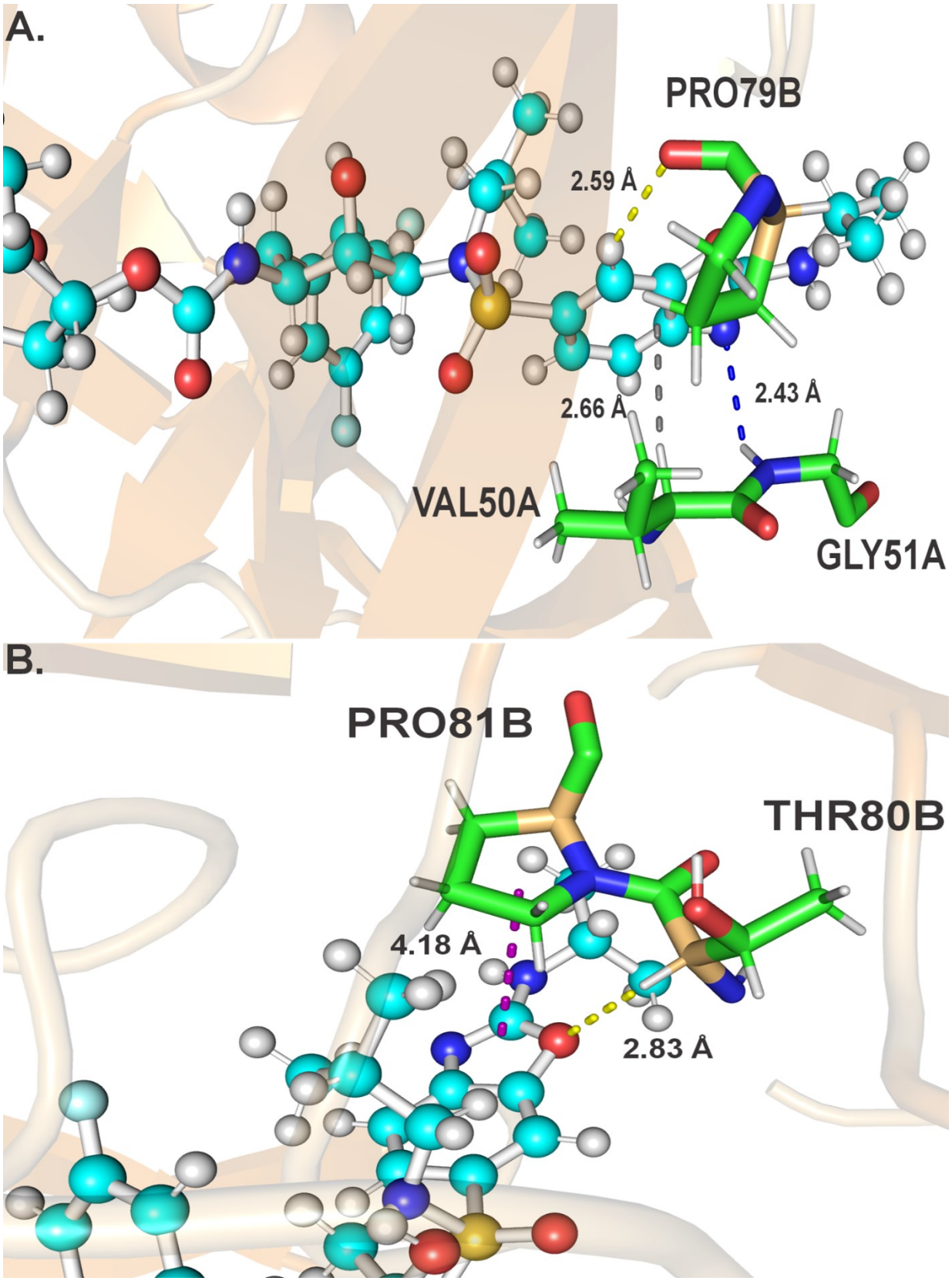
Supplementary Figure S9 - QM/MM analysis of individual replicates of PR_{MUT}-GRL-004 complex from the last 500 frames of trajectory



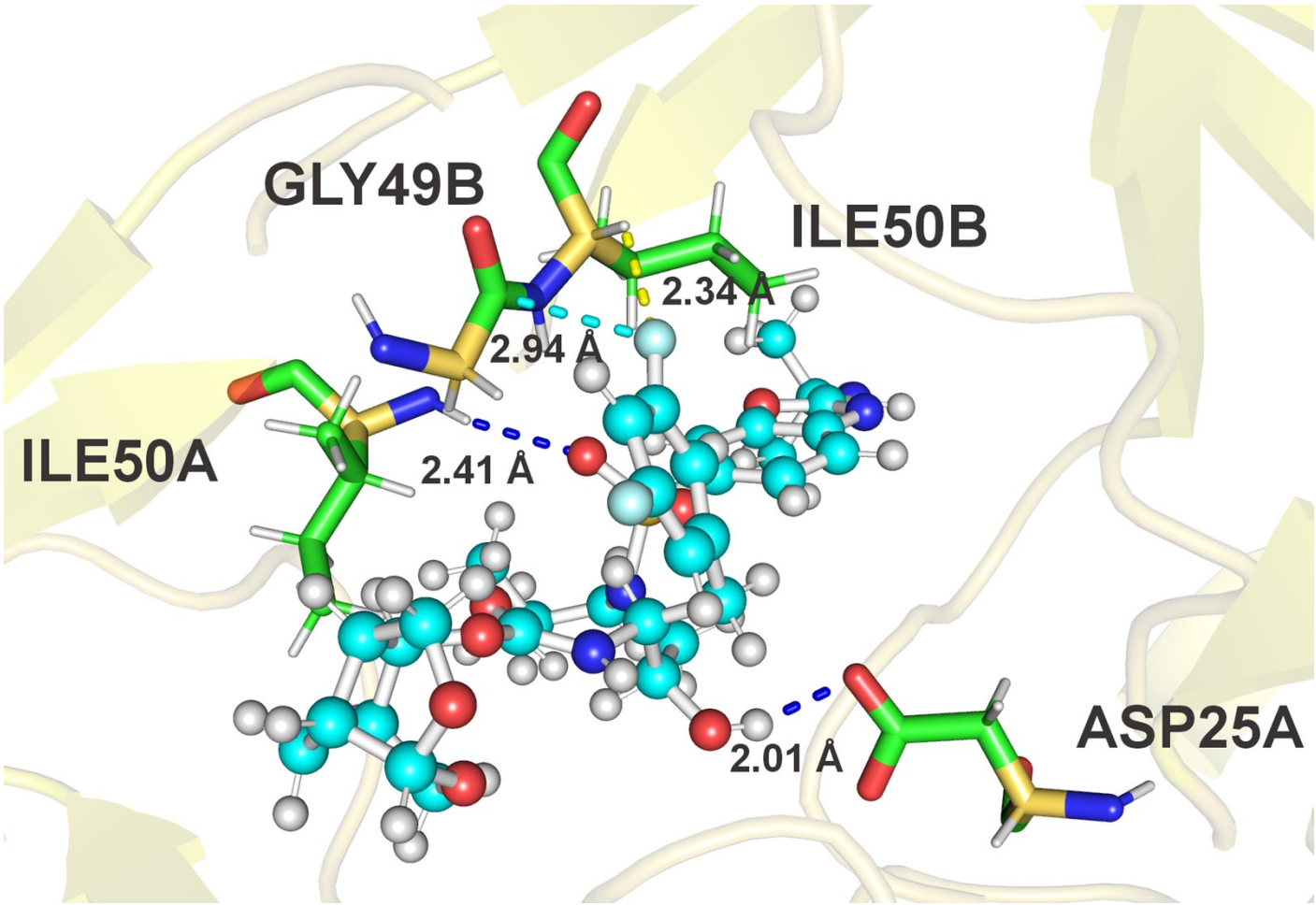
Supplementary Figure S10 – Overview of GRL-063 ligand interacting with the A. HIV-1 PR_{WT} strain and B. HIV- 1 PR_{MUT} strain.



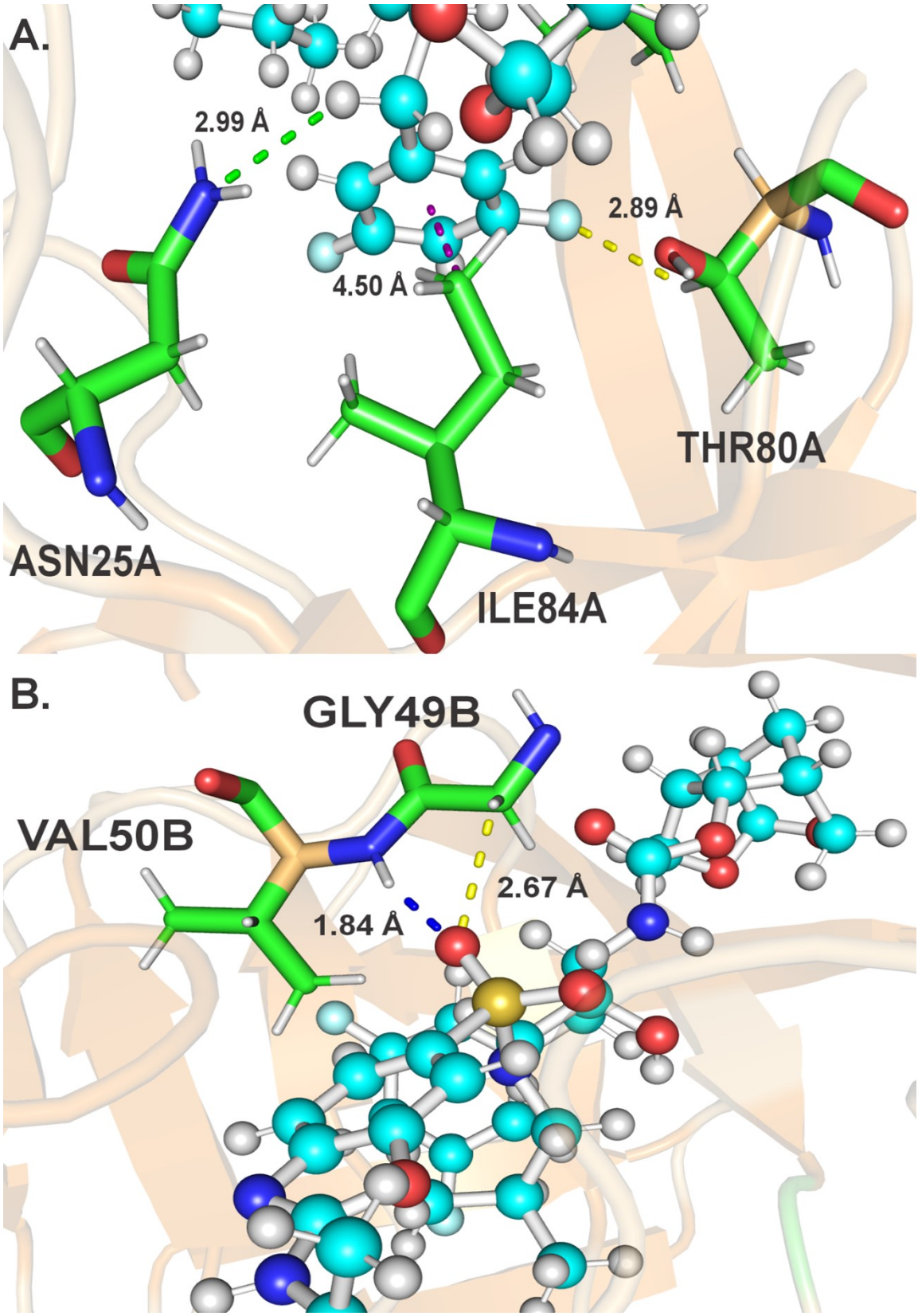
Supplementary Figure S11 – All main GRL-063 PR_{WT} residues interacting with region I of GRL-063, their distances, and respective binding properties indicated by the following colors: pink for alkyl-alkyl bonds, blue for hydrogen bonds, and yellow for non-conventional hydrogen bonds.



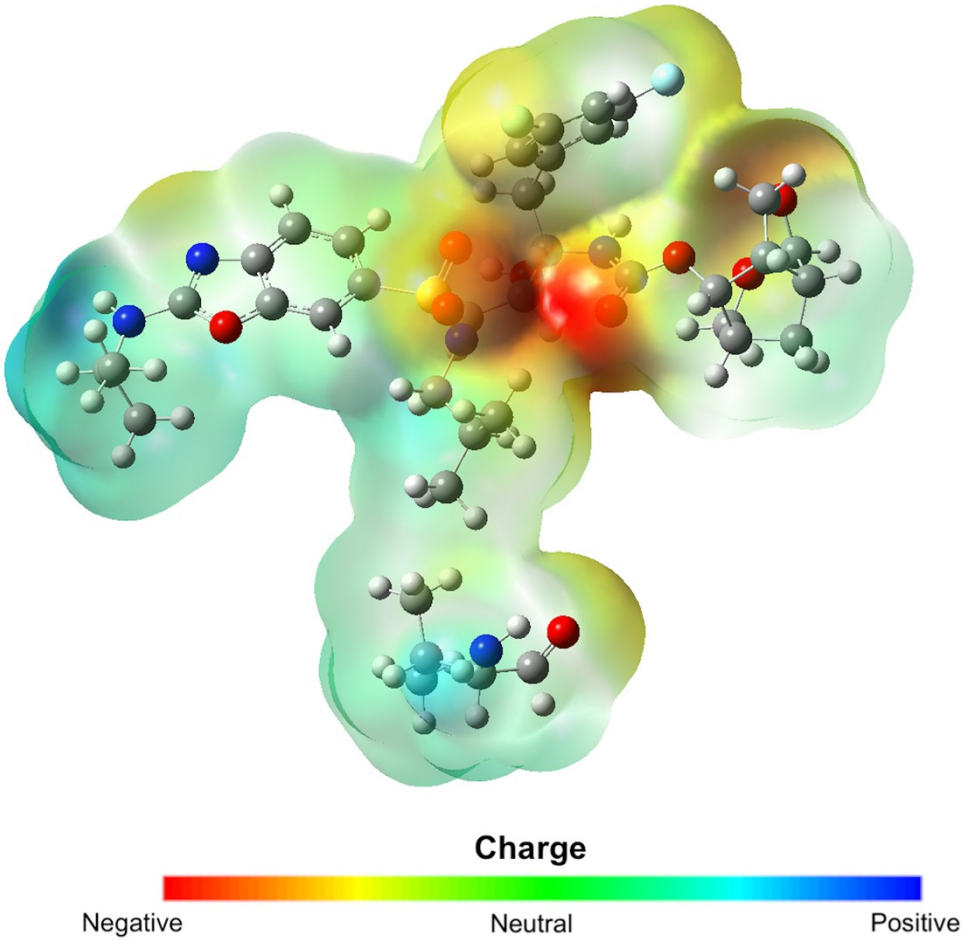
Supplementary Figure S12 – All main GRL-063 PR_{MUT} residues interacting with region I of GRL-063, their distances, and respective binding properties indicated by the following colors: blue for hydrogen bonds, yellow for non-conventional hydrogen bonds, purple for pi-alkyl and gray for pi-sigma.



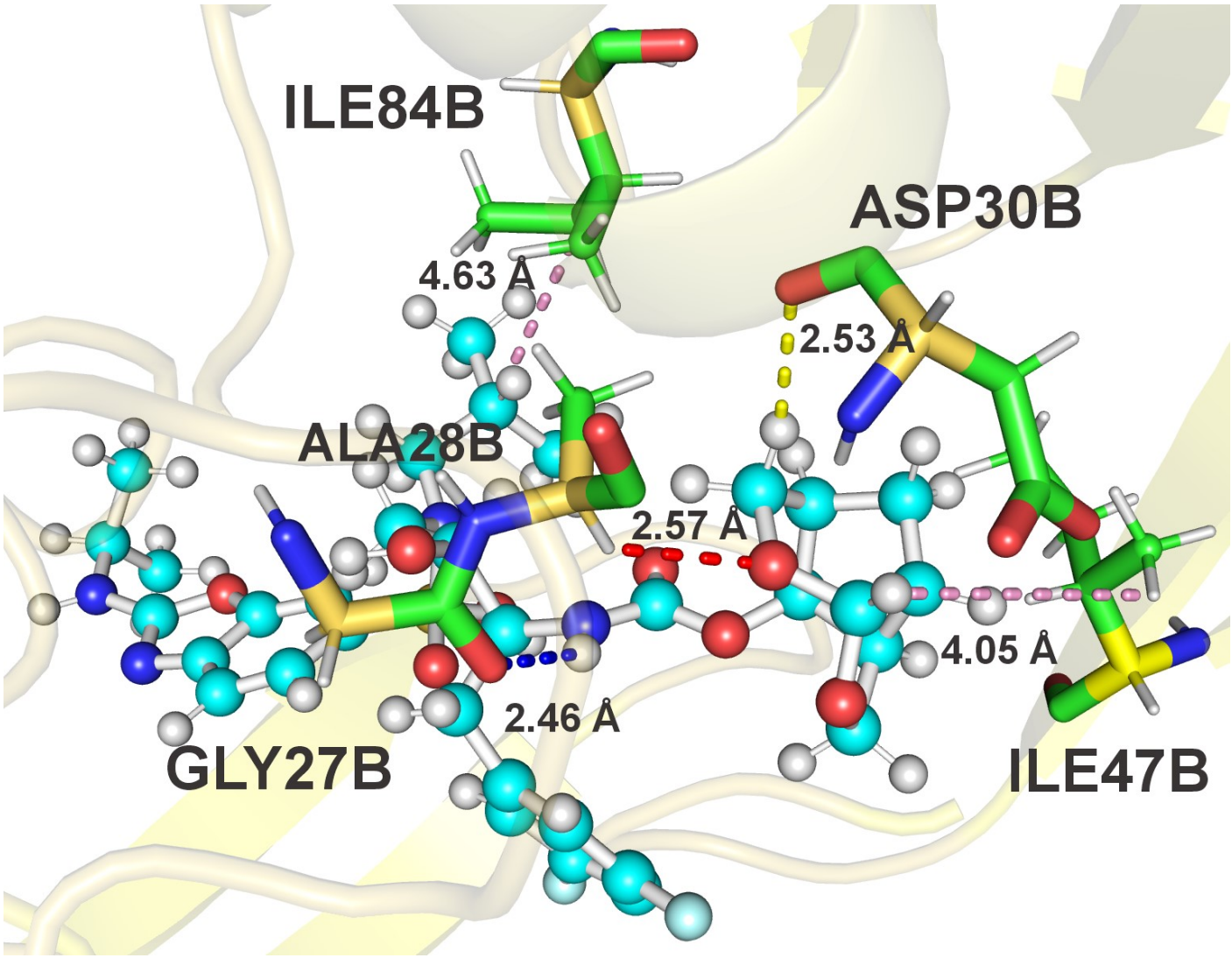
Supplementary Figure S13 – All main GRL-063 PR_{WT} residues interacting with region II of GRL-063, their distances, and respective binding properties indicated by the following colors: blue for hydrogen bonds, yellow for non-conventional hydrogen bonds, and cyan for halogen bonds.



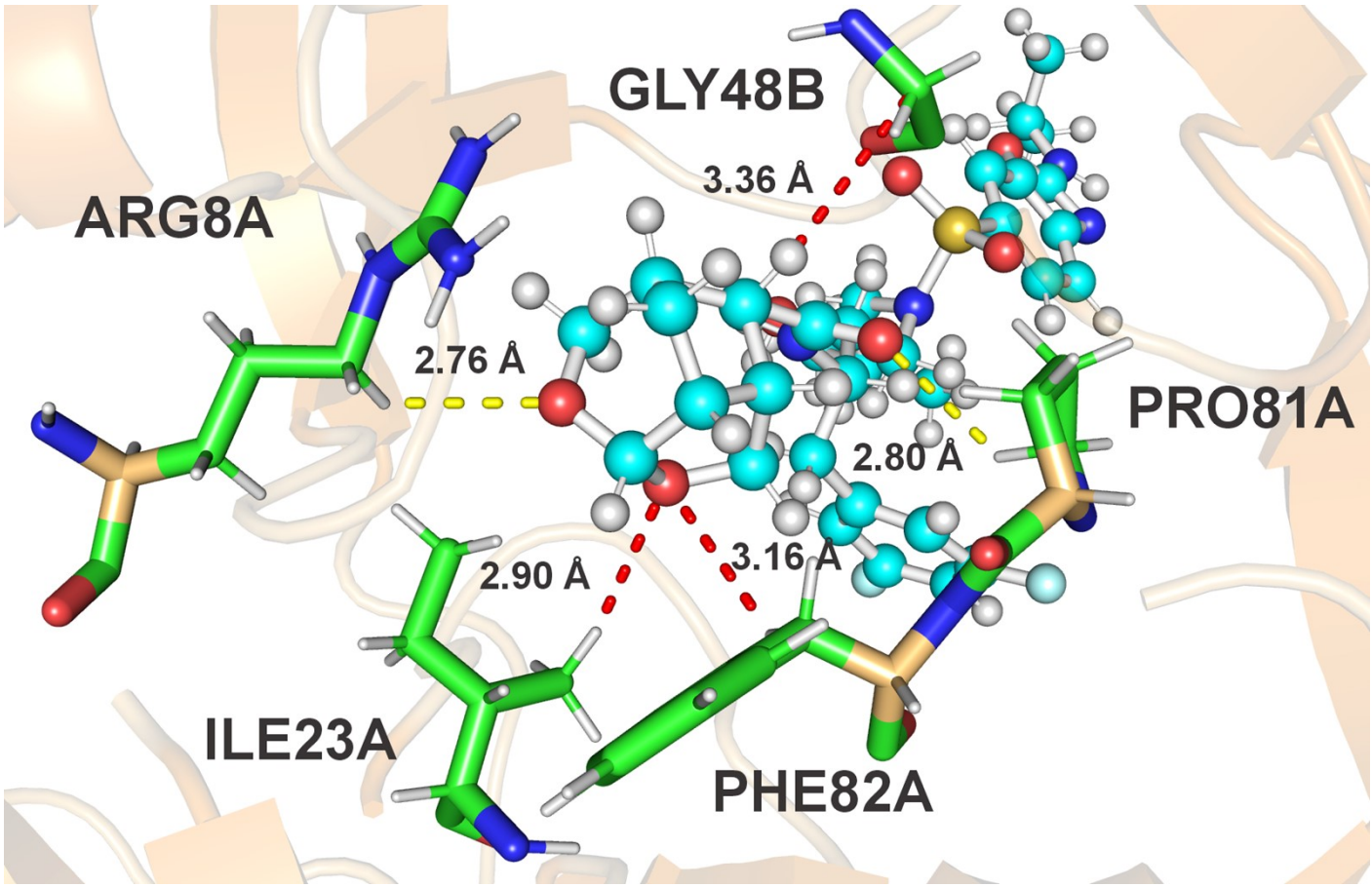
Supplementary Figure S14 – All main GRL-063 PR_{MUT} residues interacting with region II of GRL-063, their distances, and respective binding properties indicated by the following colors: blue for hydrogen bonds, yellow for non-conventional hydrogen bonds, purple for pi-alkyl and green for induced dipole.



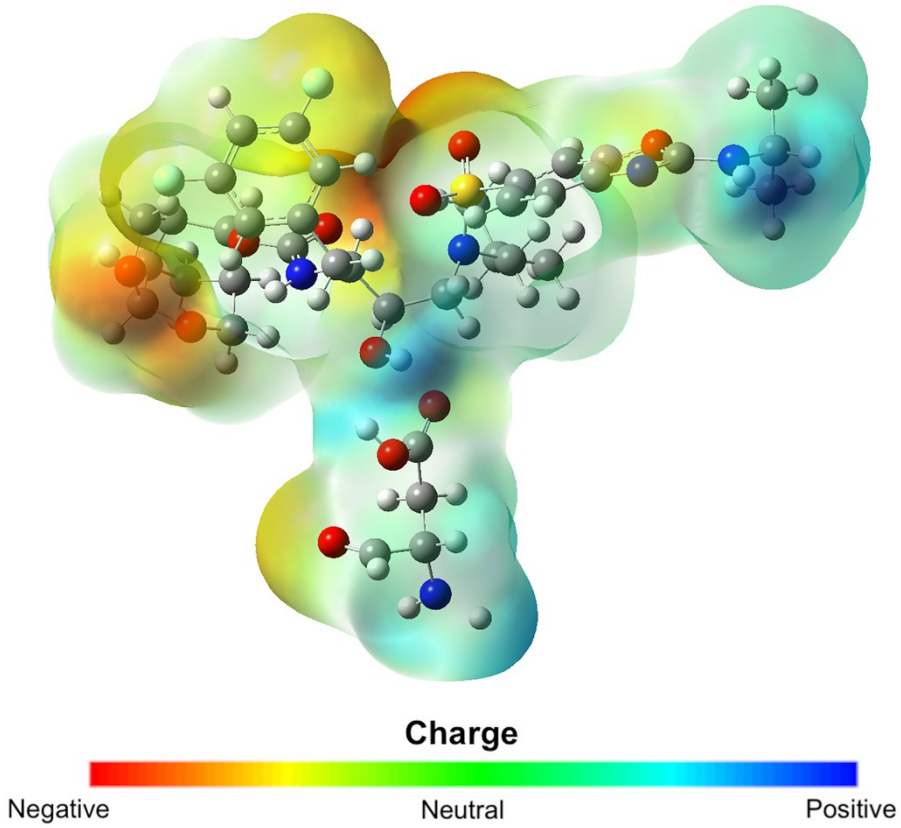
Supplementary Figure S15 – Molecular electrostatic potential (MEP) map of VAL82B and GRL-063



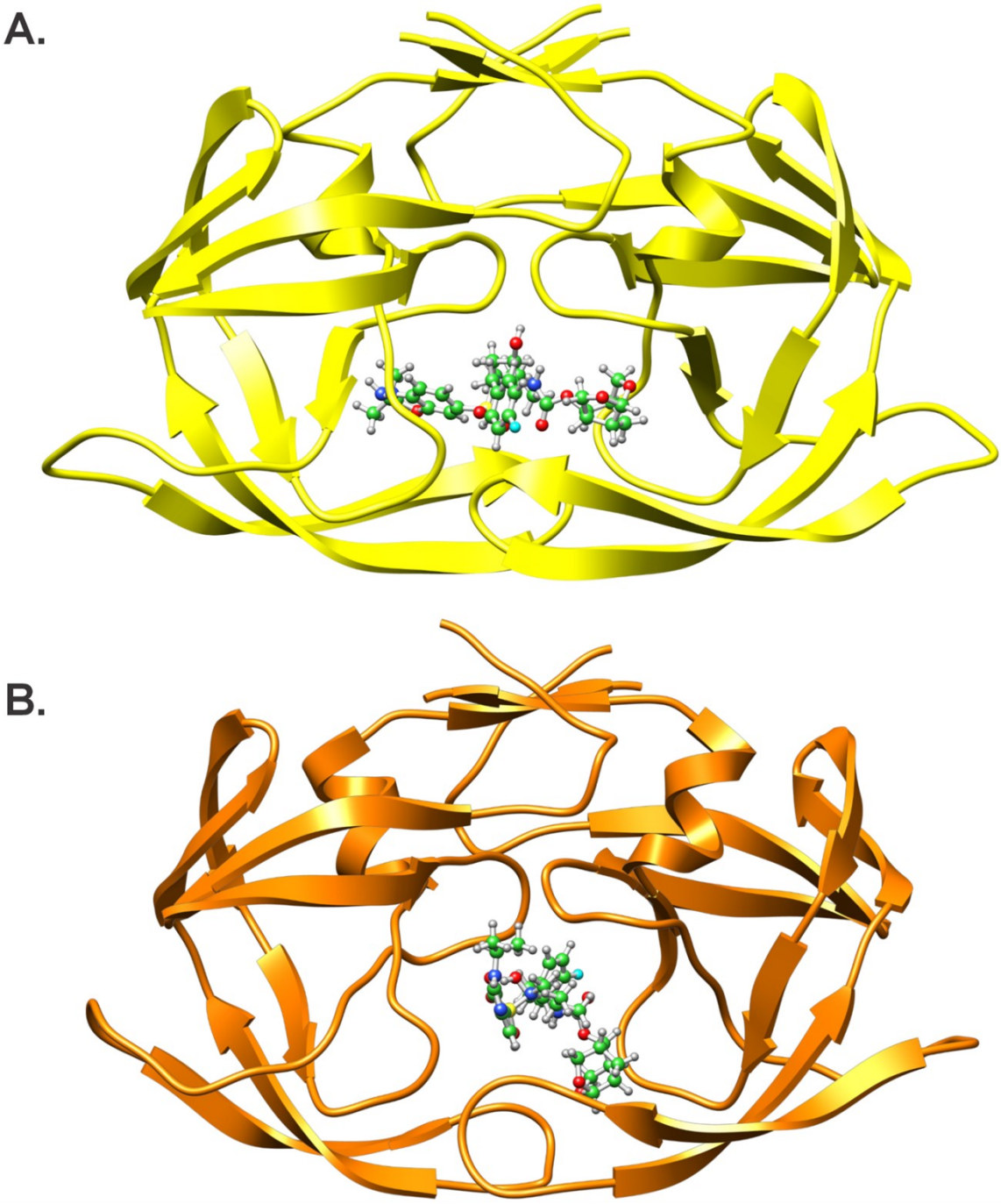
Supplementary Figure S16 – All main GRL-063 PR_{WT} residues interacting with region III of GRL-063, their distances, and respective binding properties indicated by the following colors: blue for hydrogen bonds, yellow for non-conventional hydrogen bonds, pink for alkyl-alkyl bonds, and red for dipole-dipole.



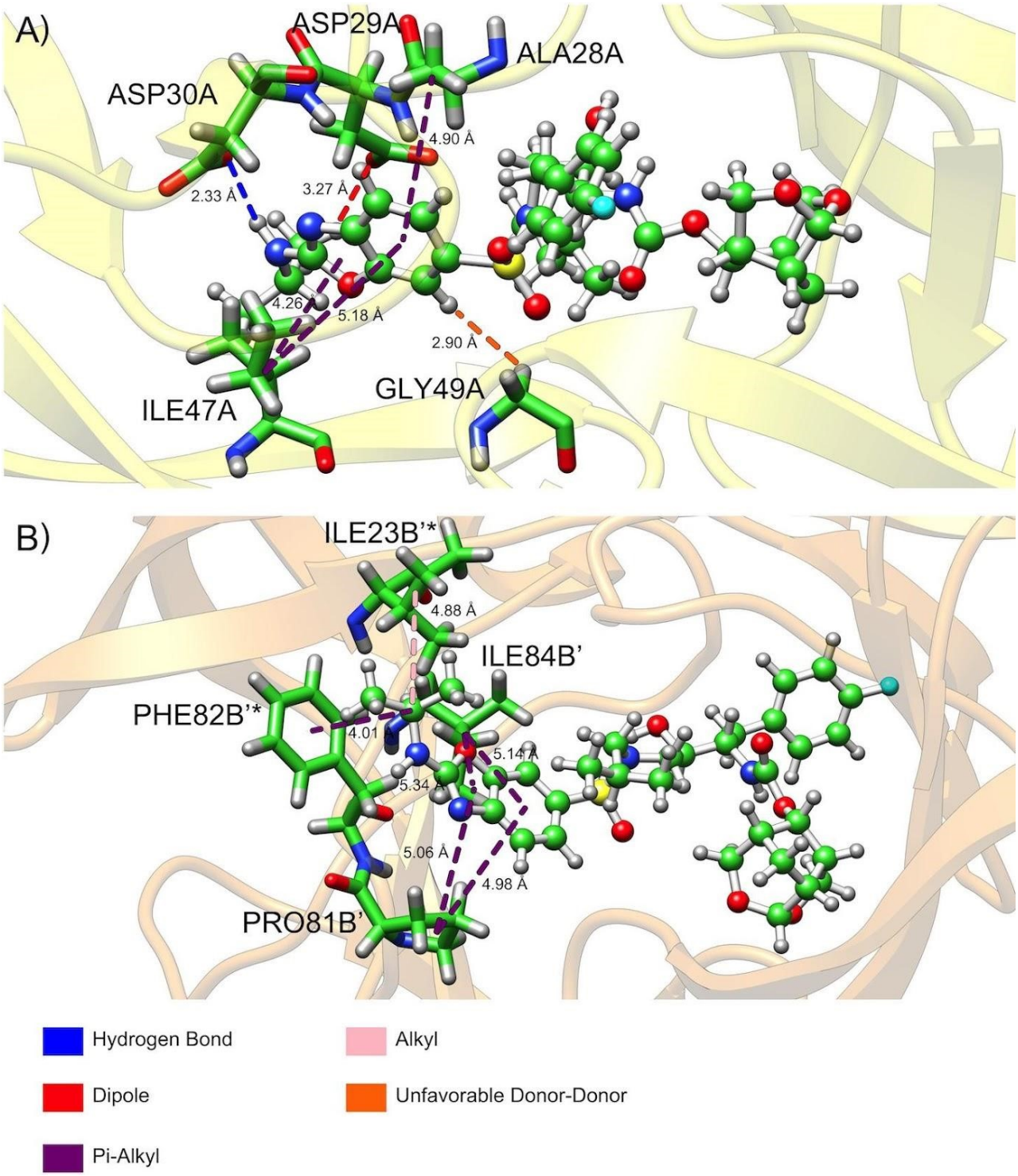
Supplementary Figure S17 – All main GRL-063 PR_{MUT} residues interacting with region III of GRL-063, their distances, and respective binding properties indicated by the following colors: yellow for non-conventional hydrogen bonds, and red for dipole-dipole



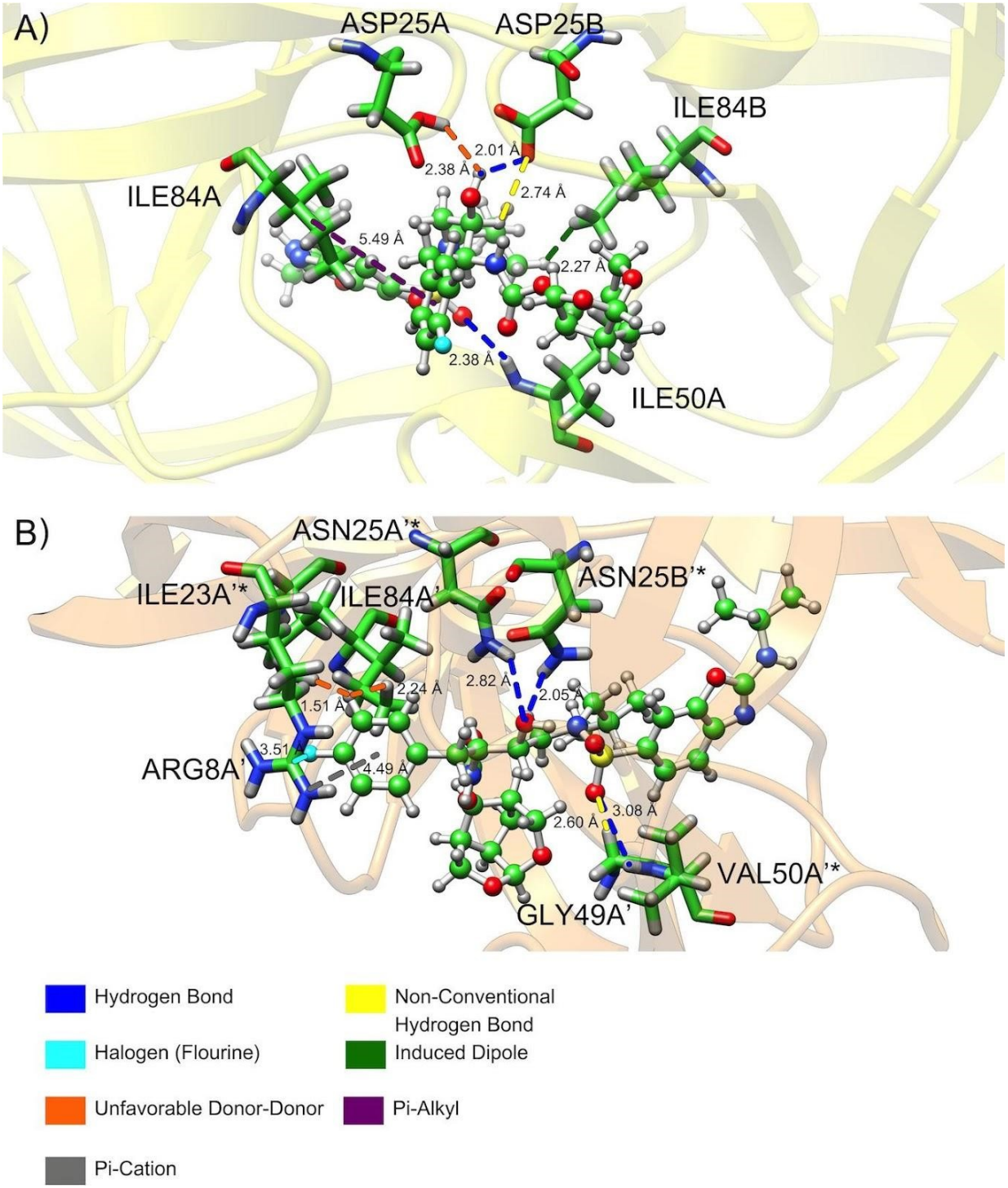
Supplementary Figure S18 – Molecular electrostatic potential (MEP) map of ASP25B and GRL-063



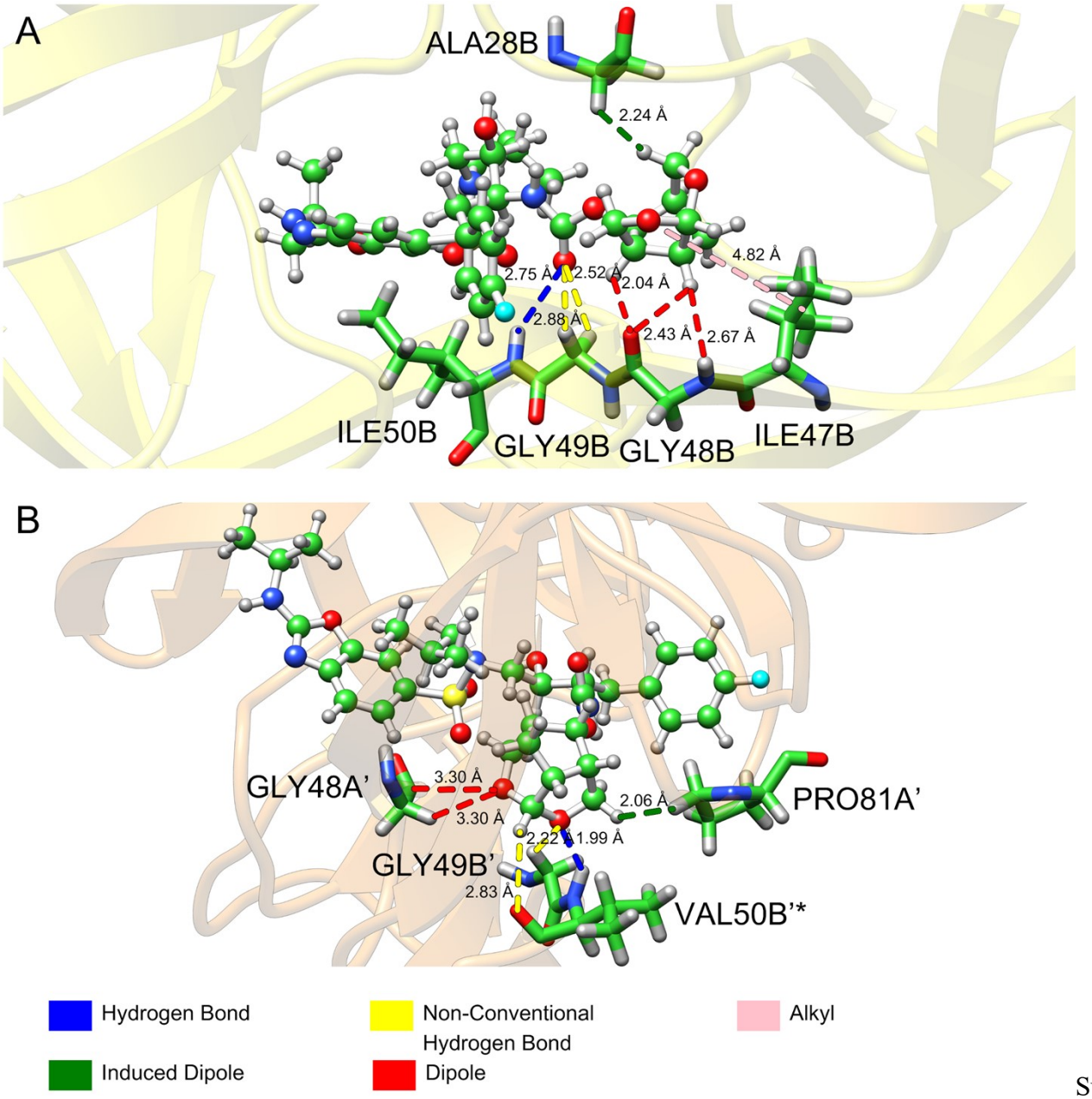
Supplementary Figure S19: Ligand-protein complexes composed by GRL-004 and each of **A)** HIV-1 PR_{WT} and **B)** HIV-1 PR_{MUT}. Different binding conformations are observed.



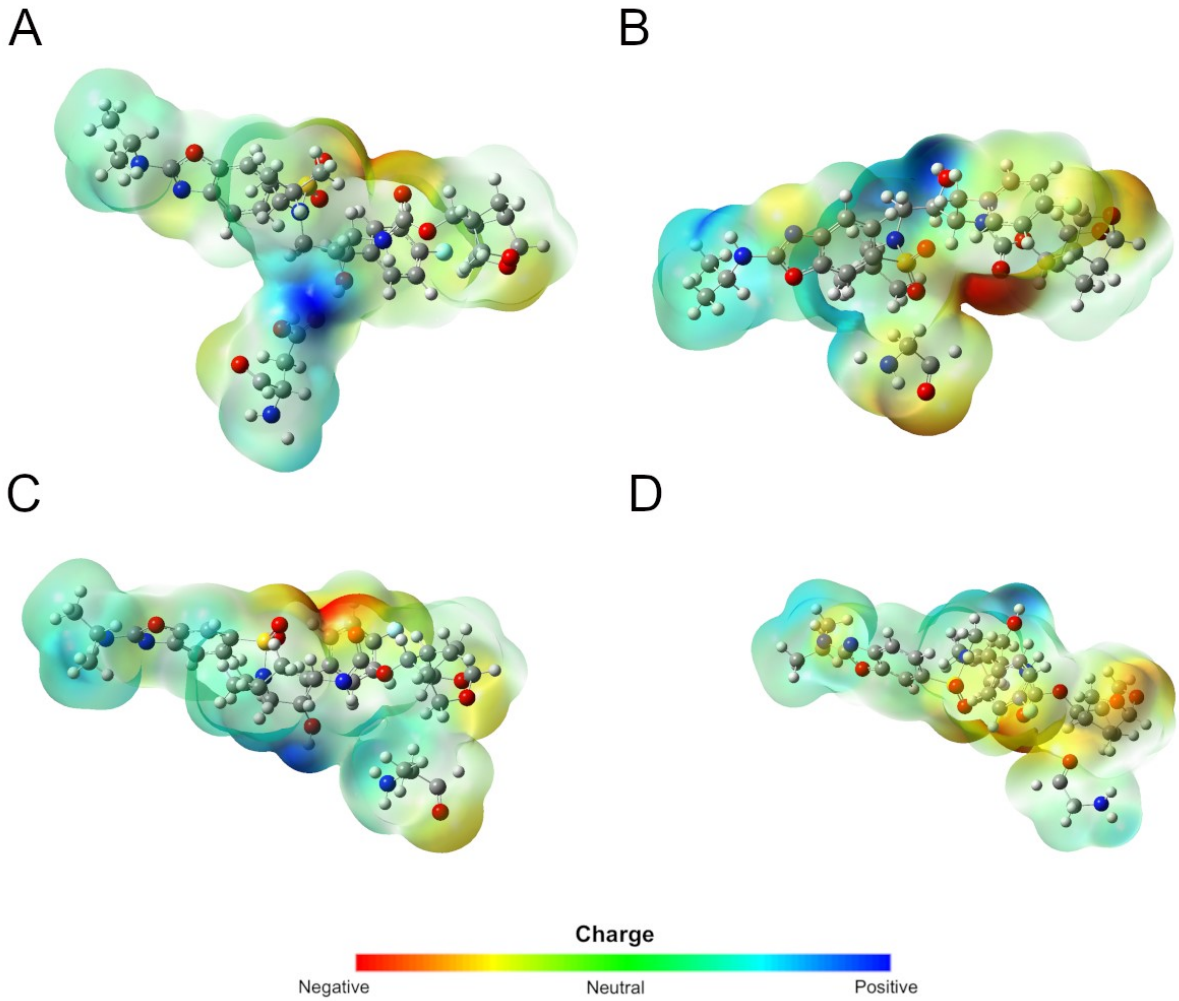
Supplementary Figure S20: Key residues promoting either intense affinity or repulsion towards region I of GRL-004 in complexes **A)** GRL-004-PR_{WT} and **B)** GRL-004-PR_{MUT}. Critical interactions are presented in dashed lines alongside the corresponding distance (in Å) and colored according to the interaction type. Hydrogen bonds are labeled in blue, alkyl interactions in pink, pi-alkyl interactions in purple, dipole forces in red, and unfavorable donor-donor interactions in orange. Interactions with one or more alkyl groups are drawn from the mass center of the group of atoms considered at each side of the interaction, resulting in distance measurements that exceed the closest contact distance.



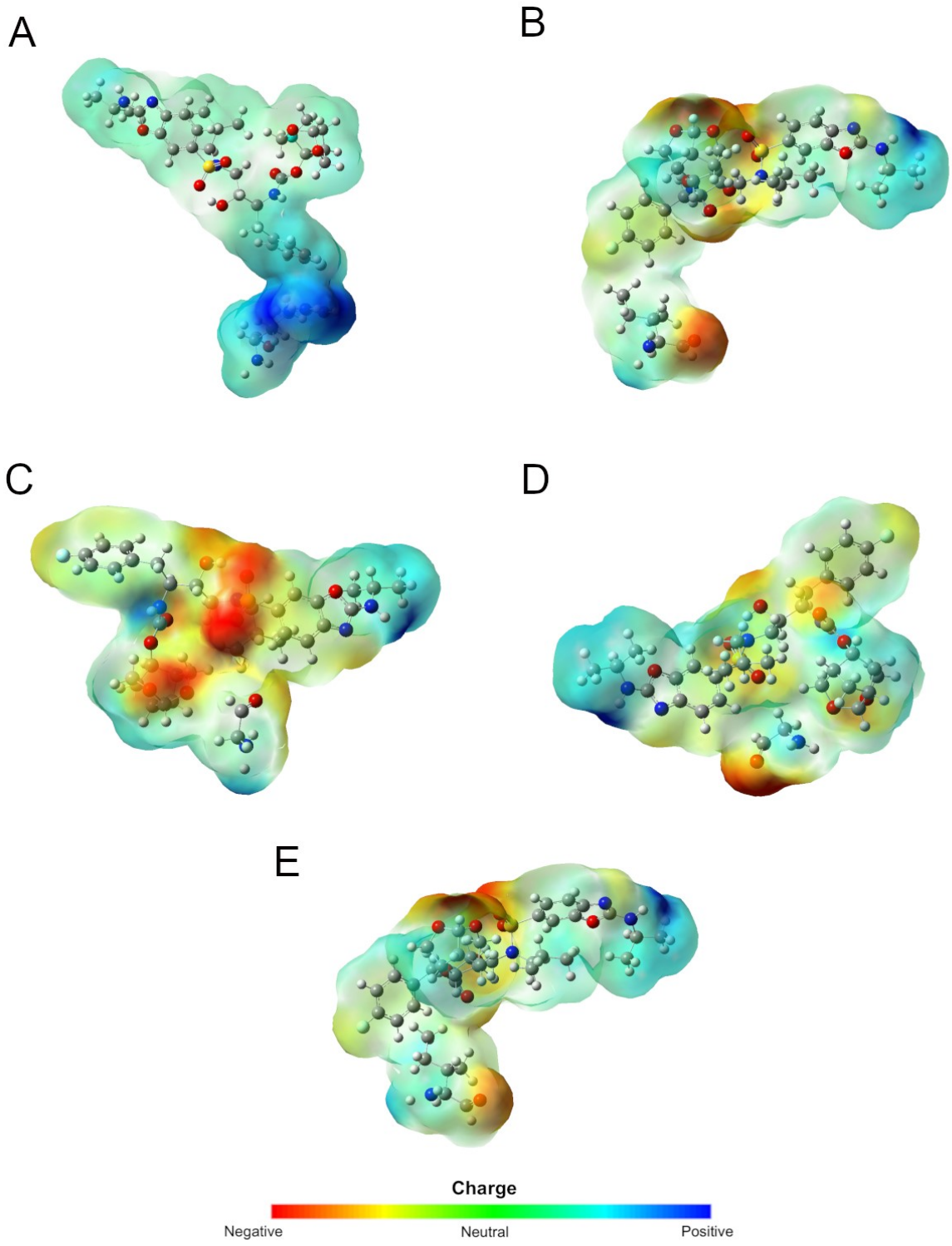
Supplementary Figure S21: Figures of the key residues from PR_{WT} **A)** and PR_{MUT} **B)** that interact with GRL-004's region II in its respective complex. Labeling follows Figure 17 with the addition of non- conventional hydrogen bonds in yellow, halogen bonds in cyan, induced-dipole forces in green, and pi-cation interactions in gray.



Supplementary Figure S22: Key residues interacting with GRL-004's region III within complexes **A)** GRL-004- PR_{WT} and **B)** GRL-004-PR_{MUT}.



Supplementary Figure S23 – Molecular electrostatic potential (MEP) map of PR_{WT} residues (A. ASP25A; B. GLY49A; C. ALA28B; D. GLY48B) and GRL-004.



Supplementary Figure S24 – Molecular electrostatic potential (MEP) map of PR_{MUT} residues (A. ARG8A'; B. ILE23A'*; C. GLY48A'; D. GLY49A'; E. ILE84A') and GRL-004.