# *In-silico* approaches towards development of model irreversible HIV-1 protease inhibitors

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## Supplementary Information

**Table S1** Mean Absolute Error (MAE) and Mean Standard Deviation (MSD) of the computed dihedral angles for the optimized lowest lying structures of Inhibitor-1 using ConfGGS/CHARMM and the optimized B3LYP/TZVP structure.

| Sl. No. | $\phi_{ijkl}$ (B3LYP/TZVP) | $\phi_{ijkl}$(ConfGGS/CHARMM) |
|---|---|---|
| 1 | 180.03 | 180.03 |
| 2 | -0.00013 | -0.17859 |
| 3 | -0.705 | -0.7294 |
| 4 | 180.03 | 179.99 |
| 5 | 30.006 | 30.158 |
| 6 | -150.03 | -149.84 |
| 7 | -60.011 | -59.834 |
| 8 | 60.011 | 60.137 |
| 9 | -180.03 | -179.95 |
| 10 | -60.194 | -60.2 |
| 11 | 179.85 | 180 |
| 12 | 82.708 | 82.364 |
| 13 | -37.314 | -37.432 |
| 14 | 7.7307 | 7.5514 |
| 15 | 149.3 | 149.28 |
| 16 | -132.25 | -132.17 |
| 17 | 9.3183 | 9.5612 |
| 18 | -3.9026 | -3.7 |
| 19 | 138.34 | 138.45 |
| 20 | -138.08 | -138.24 |
| **MAE** | | 0.12 |
| **MSD** | | 0.15 |

**Table S2** Mean Absolute Error (MAE) and Mean Standard Deviation (MSD) of the computed dihedral angles for the optimized lowest lying structures of Inhibitor-2 using ConfGGS/CHARMM and the optimized B3LYP/TZVP structure.

| Sl. No. | $\phi_{ijkl}$ (B3LYP/TZVP) | $\phi_{ijkl}$(ConfGGS/CHARMM) |
|---|---|---|
| 1 | 151.27 | 151.2 |
| 2 | -91.029 | -91.131 |
| 3 | 29.339 | 29.329 |
| 4 | 78.371 | 78.439 |
| 5 | -163.93 | -163.89 |
| 6 | -43.558 | -43.433 |
| 7 | 136.59 | 136.59 |
| 8 | -5.5083 | -5.5194 |
| 9 | 3.6048 | 3.4288 |
| 10 | 151.12 | 151.14 |
| 11 | -142.09 | -142.1 |
| 12 | 5.4322 | 5.6094 |
| 13 | -58.249 | -58.077 |
| 14 | 179.78 | 179.96 |
| 15 | 89.202 | 89.186 |
| 16 | -32.832 | -32.843 |
| 17 | -175.81 | -175.81 |
| 18 | -56.671 | -56.848 |
| 19 | 62.15 | 62.069 |
| 20 | 0.010661 | 0.15226 |
| 21 | -180.02 | -179.95 |
| 22 | -180 | -179.95 |
| 23 | 0.028844 | 0.15121 |
| **MAE** | | 0.07 |
| **MSD** | | 0.10 |

**Table S3** Mean Absolute Error (MAE) and Mean Standard Deviation (MSD) of the computed dihedral angles for the optimized lowest lying structures of Inhibitor-3 using ConfGGS/CHARMM from the optimized B3LYP/TZVP structure.

| Sl. No. | $\phi_{ijkl}$ (B3LYP/TZVP) | $\phi_{ijkl}$(ConfGGS/CHARMM) |
|---|---|---|
| 1 | 180 | 180.02 |
| 2 | -0.06303 | -0.09991 |
| 3 | 89.32 | 89.29 |
| 4 | -179.69 | -180.02 |
| 5 | 30.466 | 30.483 |
| 6 | -179.92 | -179.97 |
| 7 | -60.401 | -60.494 |
| 8 | 60.002 | 59.953 |
| 9 | 180.06 | 179.99 |
| 10 | -60.657 | -60.618 |
| 11 | 179.84 | 179.91 |
| 12 | 82.967 | 82.831 |
| 13 | -50.214 | -50.207 |
| 14 | 26.553 | 26.678 |
| 15 | 150.05 | 149.92 |

| | | |
|---|---|---|
| 16 | -131.14 | -131.32 |
| 17 | 60.552 | 60.5135 |
| 18 | -5.0076 | -5.0591 |
| 19 | 100.26 | 100.15 |
| 20 | -138.33 | -138.46 |
| 21 | -38.963 | -38.967 |
| 22 | -135.94 | -135.61 |
| 23 | 50.044 | 50.754 |
| 24 | 68.719 | 68.733 |
| 25 | -48.262 | -48.206 |
| 26 | 135.73 | 135.65 |
| **MAE** | | 0.11 |
| **MSD** | | 0.18 |

**Table S4** Mean Absolute Error (MAE) and Mean Standard Deviation (MSD) of the computed dihedral angles for the optimized lowest lying structures of Inhibitor-4 using ConfGGS/CHARMM from the optimized B3LYP/TZVP structure.

| **Sl. No.** | **$\phi_{ijkl}$ (B3LYP/TZVP)** | **$\phi_{ijkl}$(ConfGGS/CHARMM)** |
|---|---|---|
| 1 | -180.03 | -179.93 |
| 2 | -0.772 | -0.74409 |
| 3 | 0.000154 | 0.05842 |
| 4 | -180.03 | -179.93 |
| 5 | 30.006 | 30.151 |
| 6 | -150.03 | -150.01 |
| 7 | -60.011 | -59.874 |
| 8 | 60.011 | 60.029 |
| 9 | 180 | 180.03 |
| 10 | -60.171 | -59.907 |
| 11 | 179.87 | 179.93 |
| 12 | 82.795 | 82.636 |
| 13 | -37.227 | -37.386 |
| 14 | 7.7311 | 7.7432 |
| 15 | 149.46 | 149.31 |
| 16 | -132.36 | -132.27 |
| 17 | 9.3661 | 9.6059 |
| 18 | -6.569 | -6.6521 |
| 19 | 135.84 | 135.78 |
| 20 | -135.55 | -135.67 |
| 21 | -38.536 | -38.745 |
| 22 | 81.487 | 81.277 |
| 23 | -158.56 | -158.8 |
| 24 | 38.536 | 38.608 |
| 25 | 158.56 | 158.63 |
| 26 | -81.487 | -81.449 |
| **MAE** | | 0.11 |
| **MSD** | | 0.18 |

**Table S5** Mean Absolute Error (MAE) and Mean Standard Deviation (MSD) of the computed dihedral angles for the optimized lowest lying structures of Inhibitor-5 using ConfGGS/CHARMM from the optimized B3LYP/TZVP structure.

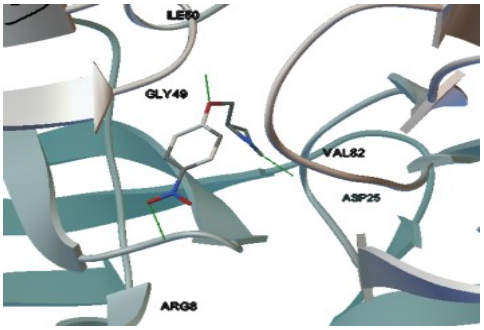
| Sl. No. | $\phi_{ijkl}$ (B3LYP/TZVP) | $\phi_{ijkl}$(ConfGGS/CHARMM) |
|---|---|---|
| 1 | 180.03 | 179.96 |
| 2 | -0.00025 | -0.02587 |
| 3 | -0.0422 | -0.10822 |
| 4 | 180.03 | 180.02 |
| 5 | 30.006 | 30.137 |
| 6 | -150.03 | -150.16 |
| 7 | -60.011 | -60.009 |
| 8 | 60.011 | 60.041 |
| 9 | -180.03 | -179.88 |
| 10 | -60.19 | -60.028 |
| 11 | 179.86 | 180 |
| 12 | 82.739 | 82.425 |
| 13 | -37.283 | -37.551 |
| 14 | 7.8374 | 7.5228 |
| 15 | 149.95 | 149.97 |
| 16 | -132.15 | -131.97 |
| 17 | 9.9539 | 10.48 |
| 18 | 9.0578 | 9.0246 |
| 19 | 147.85 | 147.89 |
| 20 | -138.35 | -138.54 |
| 21 | 154.44 | 154.42 |
| 22 | -25.599 | -25.558 |
| 23 | 85.61 | 85.644 |
| 24 | -94.424 | -94.337 |
| **MAE** | | 0.12 |
| **MSD** | | 0.17 |

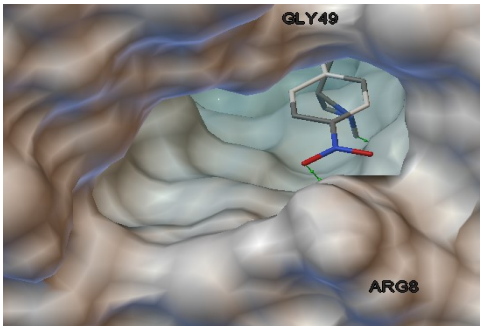
**Table S6** Mean Absolute Error (MAE) and Mean Standard Deviation (MSD) of the computed dihedral angles for the optimized lowest lying structures of Inhibitor-6 using ConfGGS/CHARMM from the optimized B3LYP/TZVP structure.

| Sl. No. | $\phi_{ijkl}$ (B3LYP/TZVP) | $\phi_{ijkl}$(ConfGGS/CHARMM) |
|---|---|---|
| 1 | 180.03 | 179.74 |
| 2 | 0.2095 | 0.12064 |
| 3 | 0.9535 | 0.12065 |
| 4 | 180.03 | 179.99 |
| 5 | 30.006 | 29.901 |
| 6 | -150.03 | -150.19 |
| 7 | -60.011 | -60.182 |
| 8 | 60.011 | 59.869 |
| 9 | -180.03 | -179.94 |

| | | |
|---|---|---|
| 10 | -60.19 | -60.248 |
| 11 | 179.86 | 180 |
| 12 | 82.739 | 82.564 |
| 13 | -37.283 | -37.189 |
| 14 | 7.8374 | 7.6087 |
| 15 | 149.95 | 150 |
| 16 | -132.15 | -132.29 |
| 17 | 9.9539 | 10.093 |
| 18 | 9.0578 | 9.07 |
| 19 | 147.85 | 147.82 |
| 20 | -138.35 | -138.47 |
| 21 | 154.44 | 154.37 |
| 22 | -25.599 | -25.479 |
| 23 | 85.61 | 85.496 |
| 24 | -94.424 | -94.35 |
| **MAE** | | 0.14 |
| **MSD** | | 0.19 |

Conformer-1

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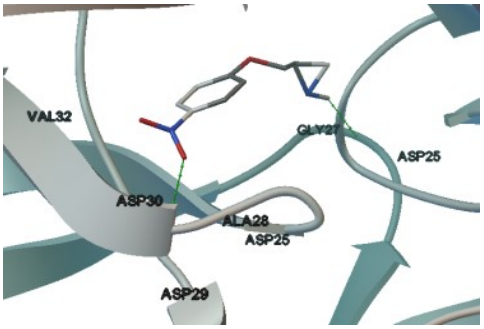


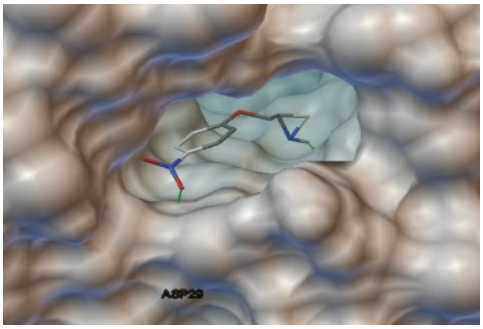

| | |
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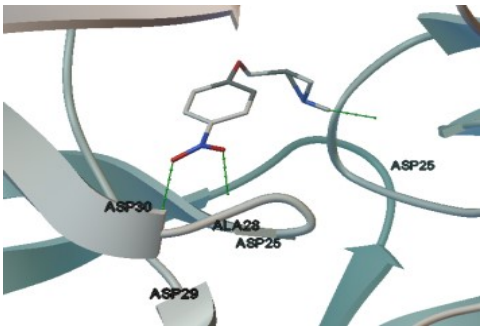
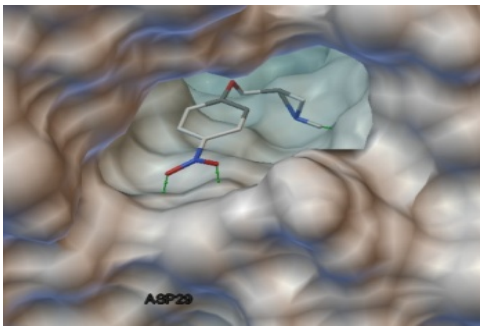
|  |  |
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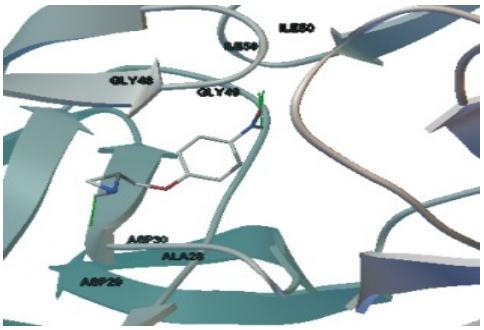
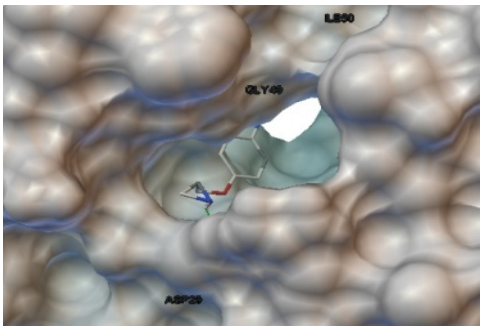
|  |  |
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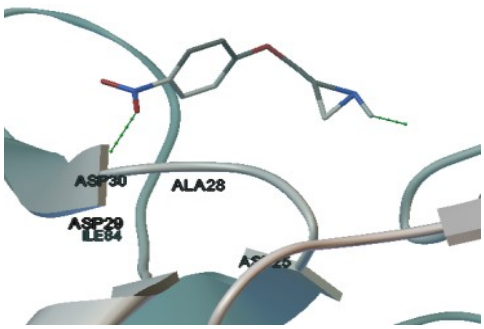
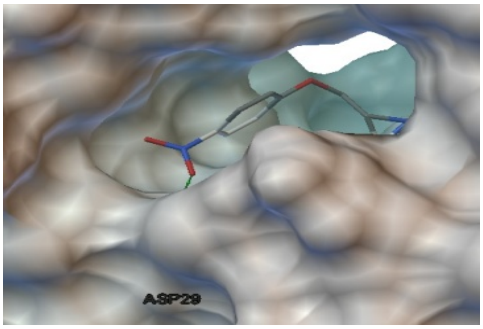
|  |  |
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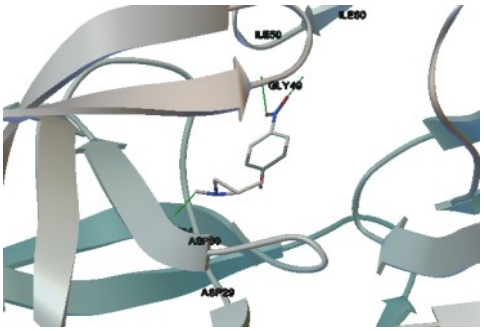
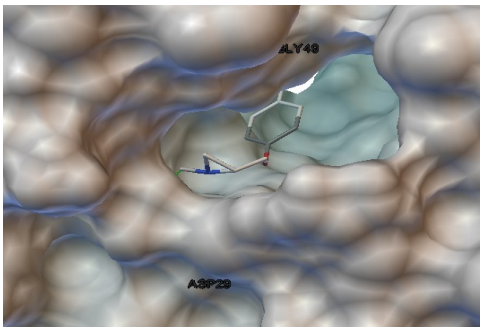
|  |  |

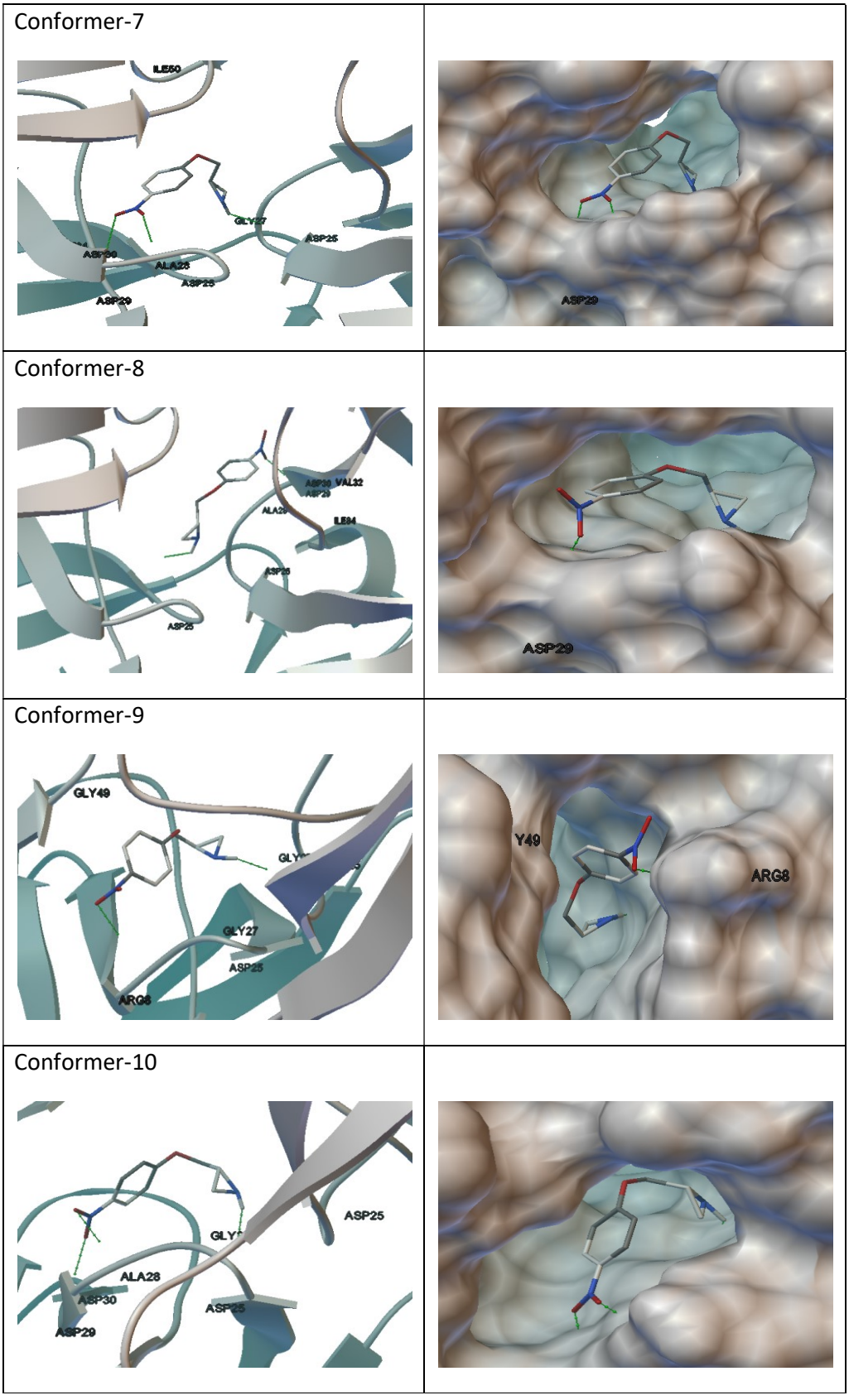



**Fig. S1** Molecular docking interaction of Inhibitor-1 with HIV-1 Protease.

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|---|---|
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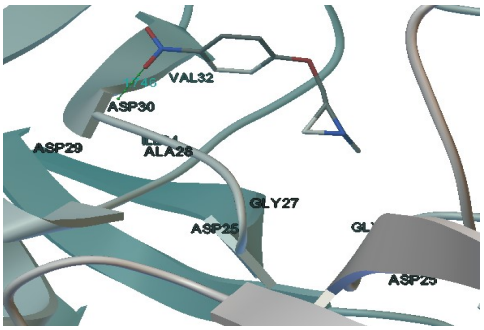
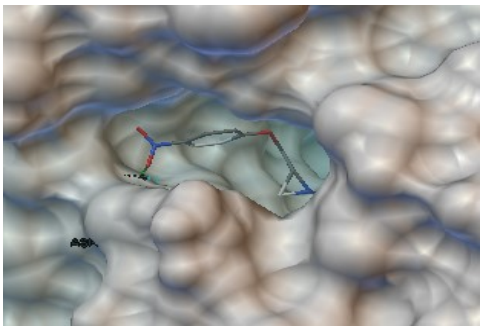
|  |  |
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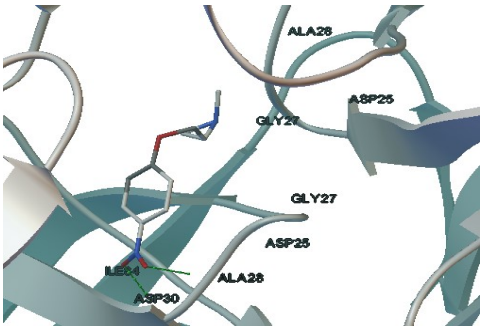
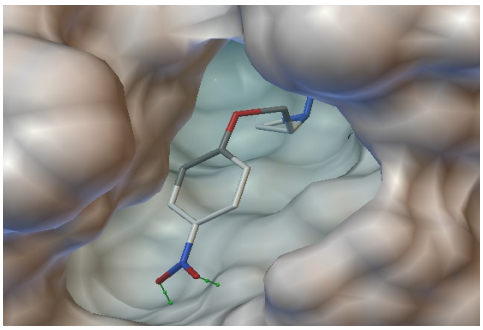
|  |  |
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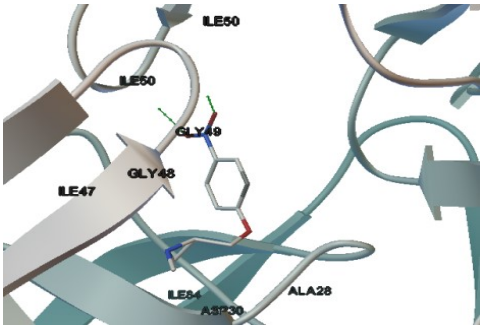
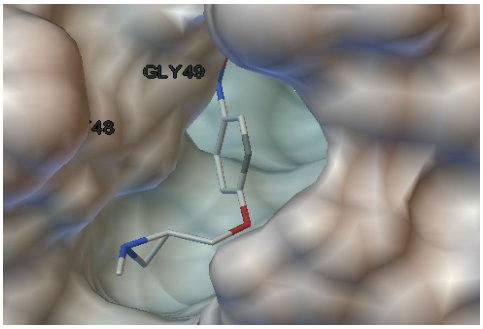
|  |  |
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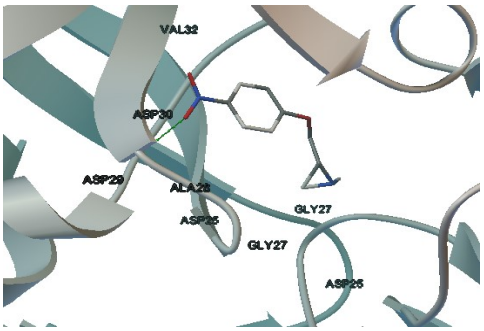
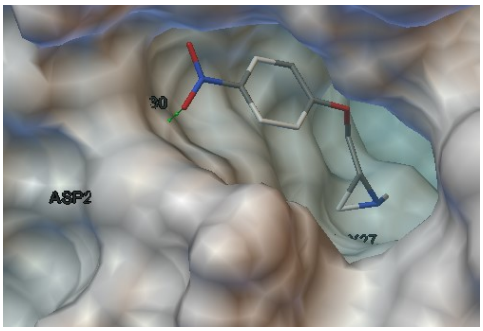
|  |  |
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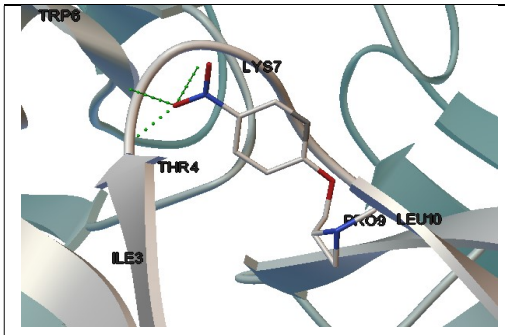


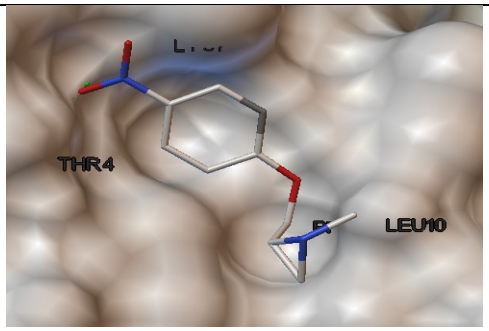


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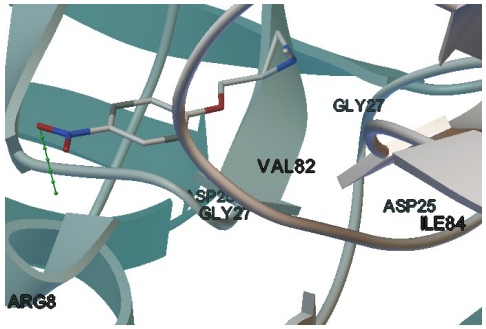


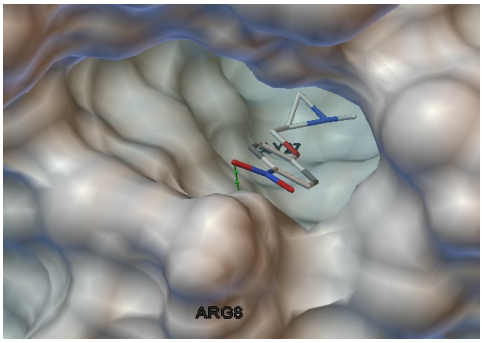


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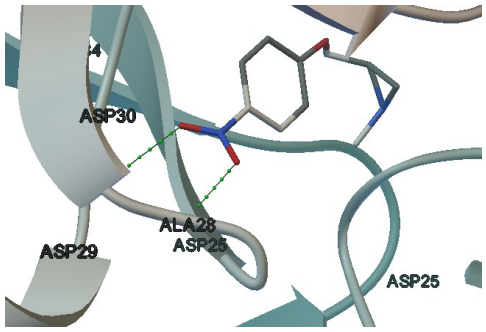


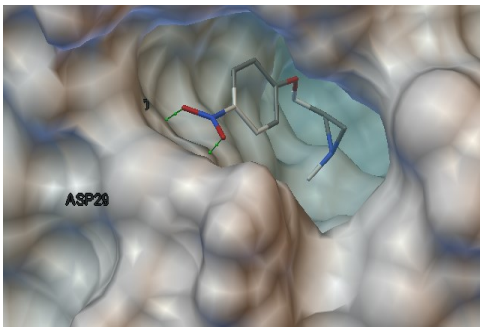


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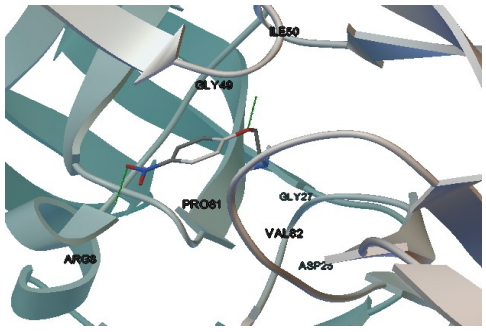


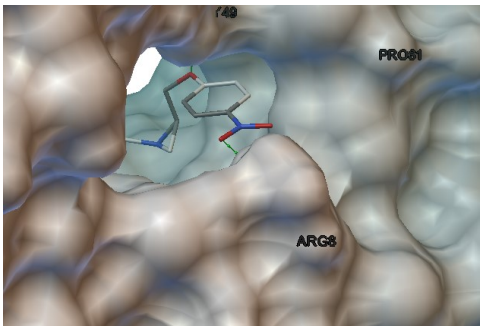


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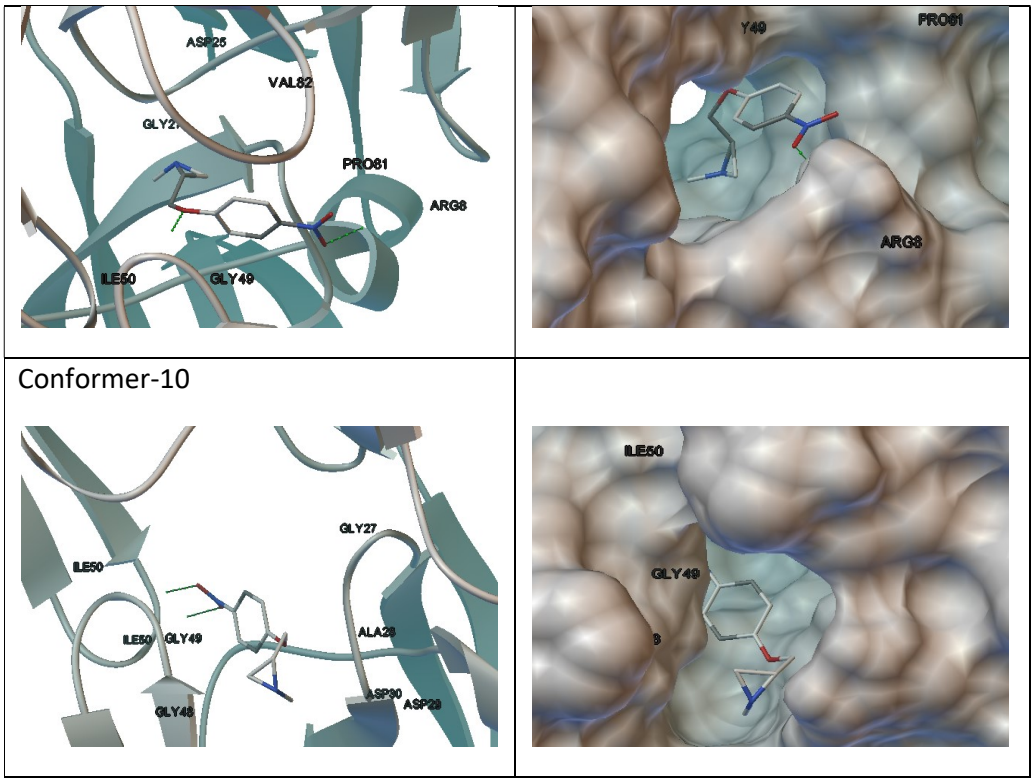
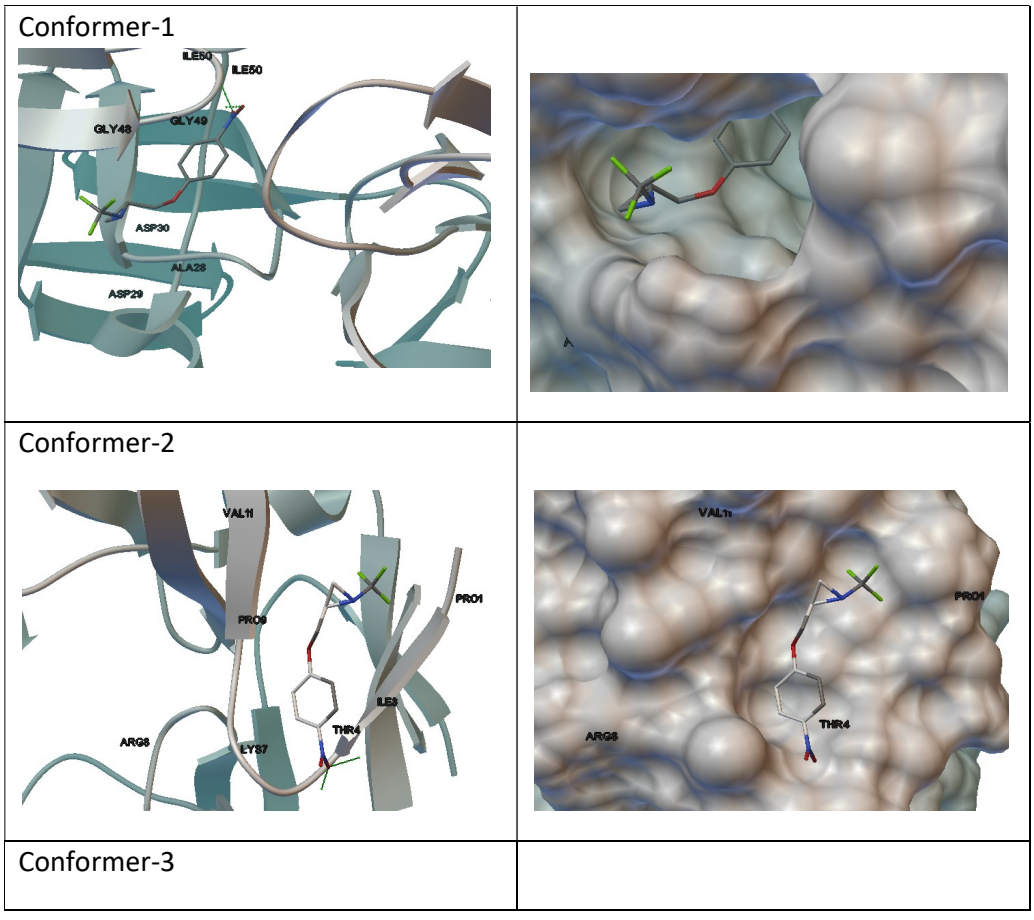



**Fig. S2** Molecular docking interaction of Inhibitor-2 with HIV-1 Protease.



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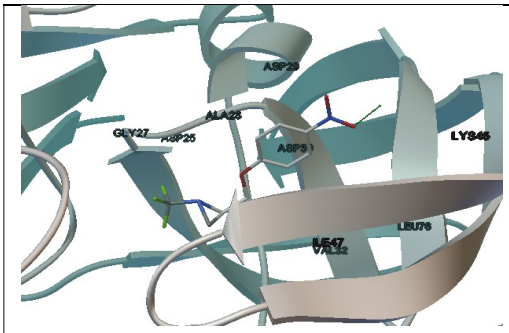
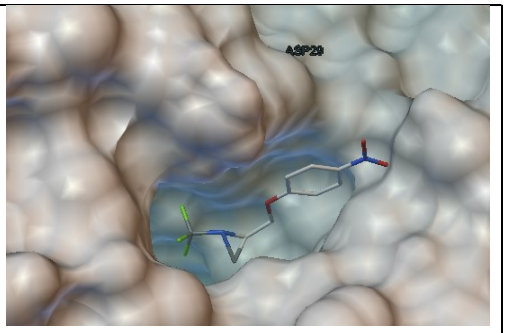
|   |   |
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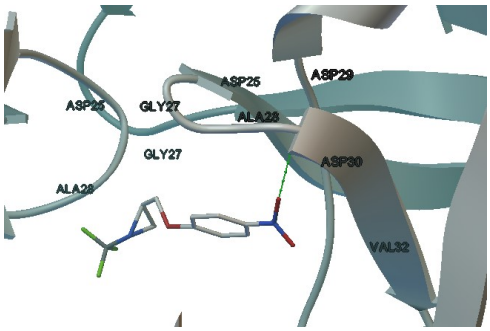
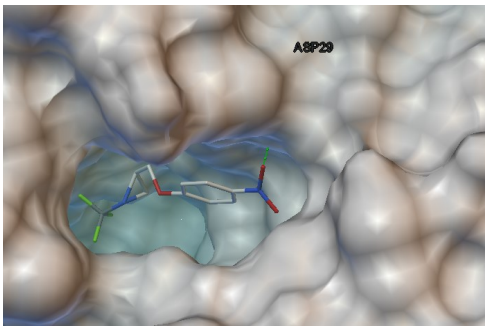
|   |   |
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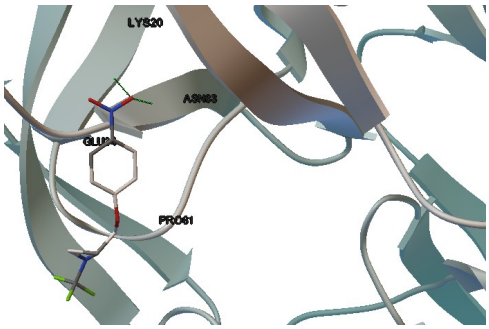
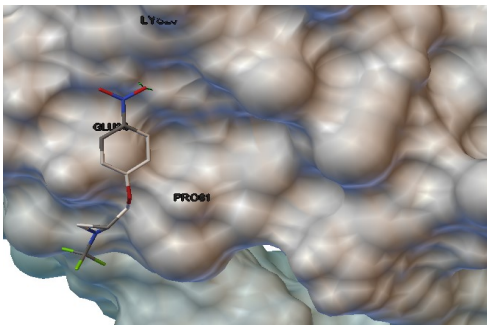
|   |   |
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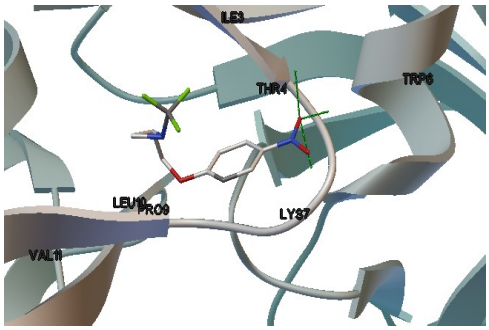
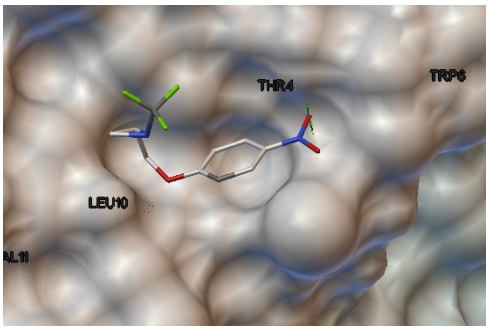
|   |   |
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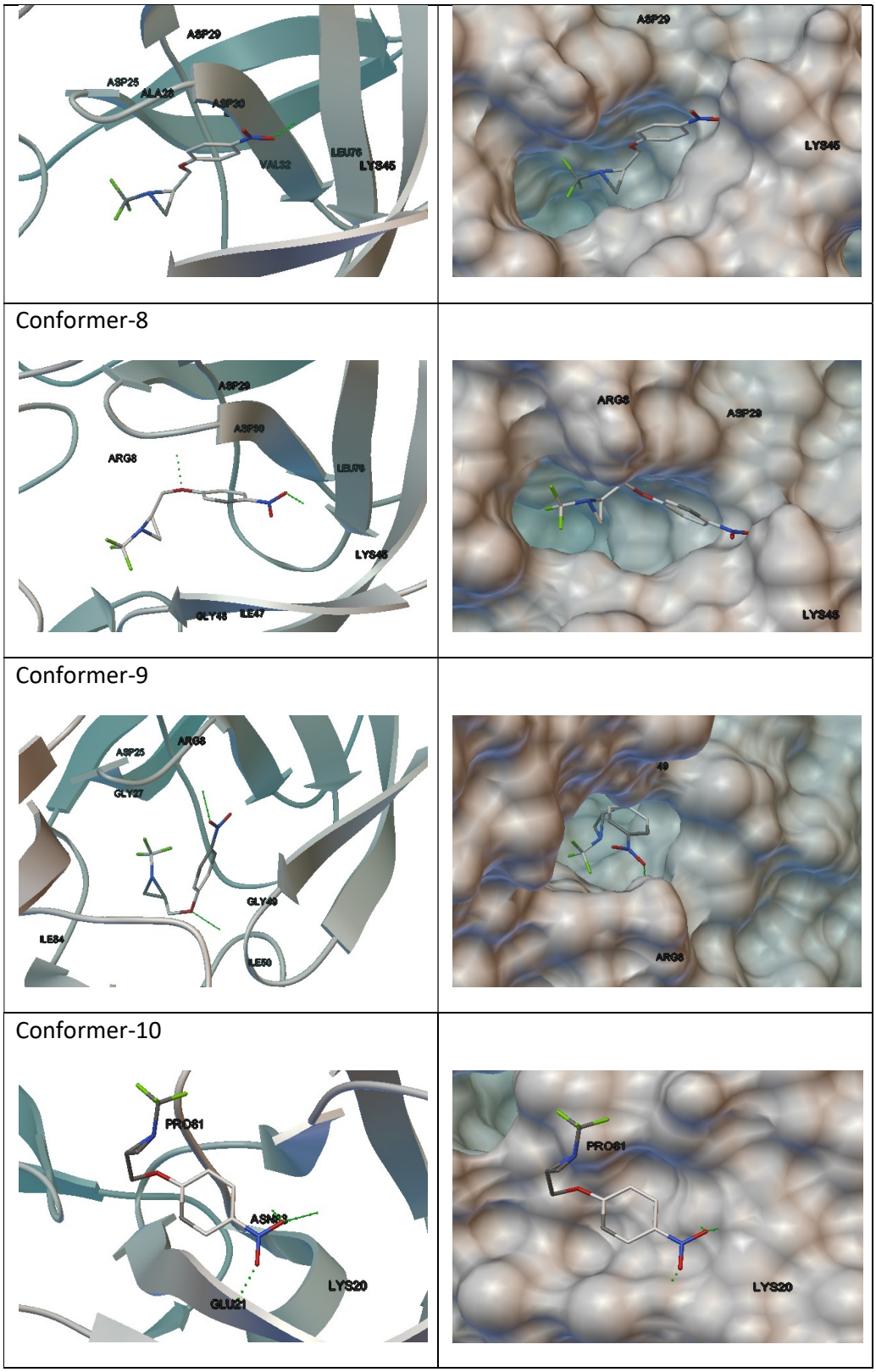


**Fig. S3** Molecular docking interaction of Inhibitor-3 with HIV-1 Protease.

| | |
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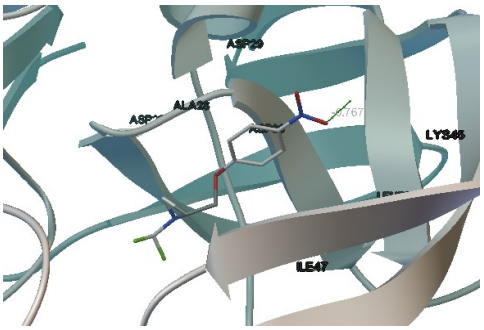
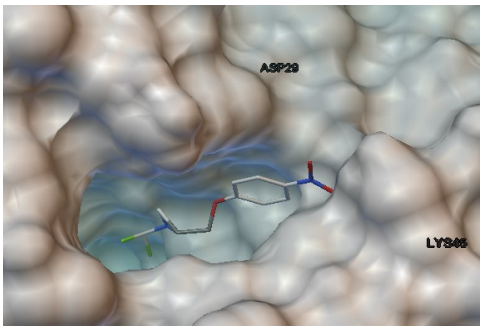
|  |  |
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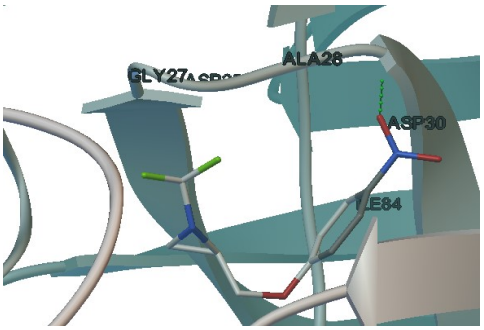
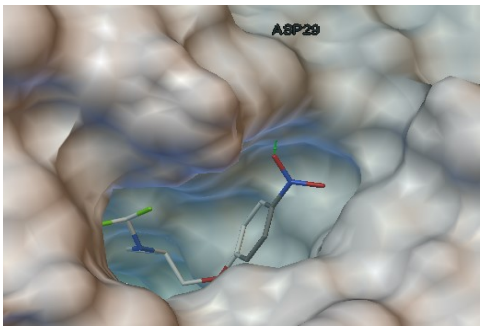
|  |  |
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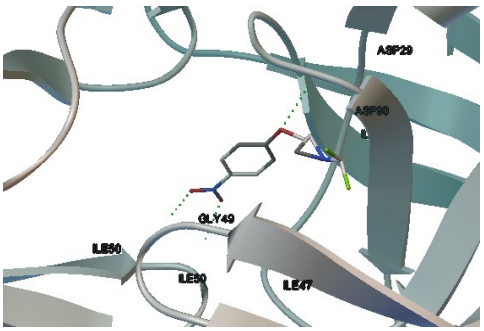
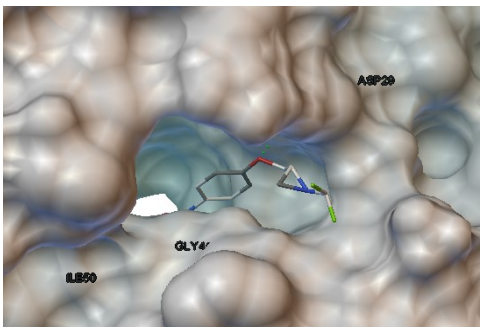
|  |  |
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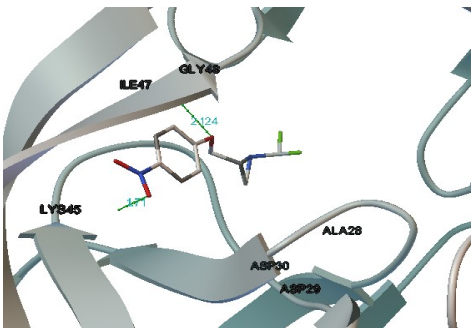
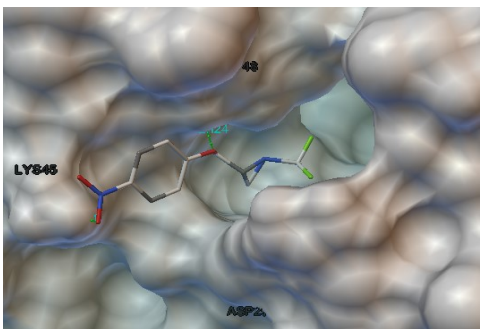
|  |  |
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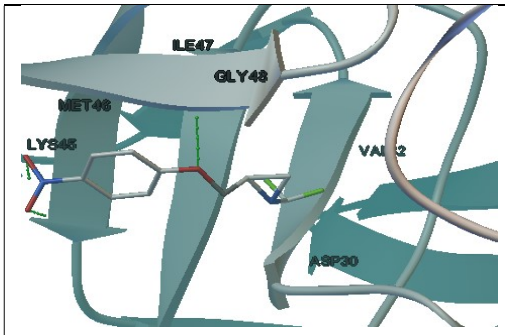
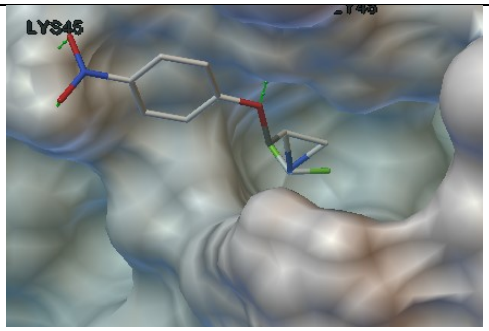
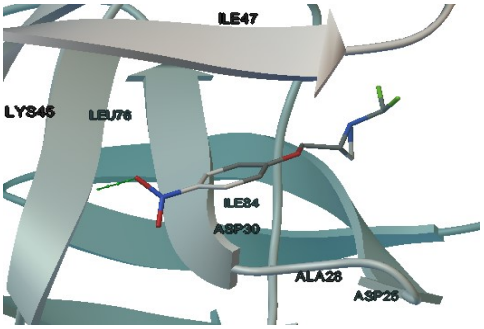
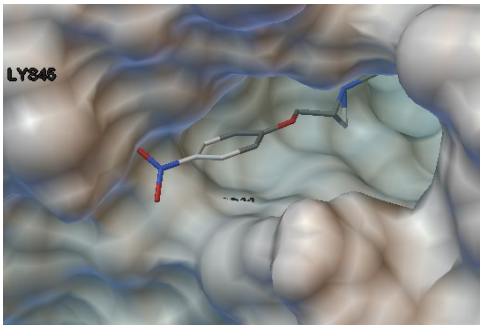


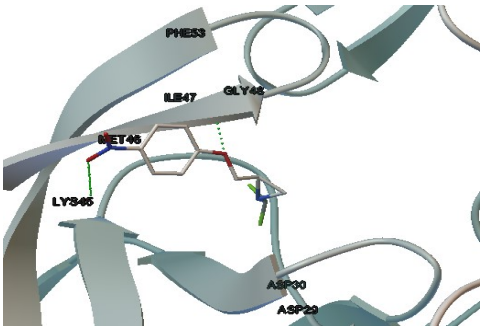



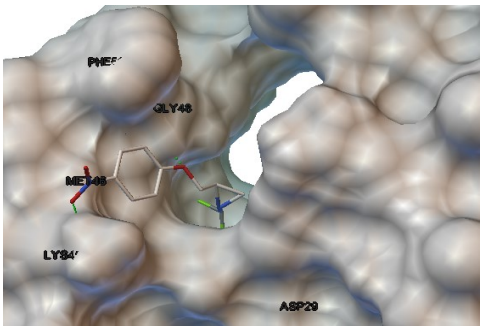

Conformer-6




Conformer-7

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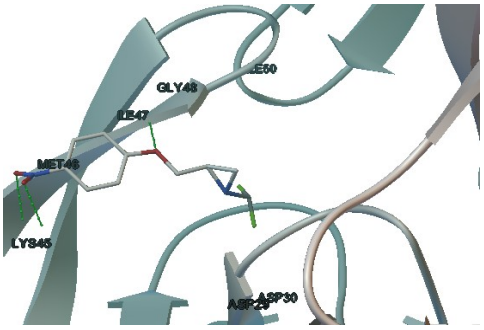
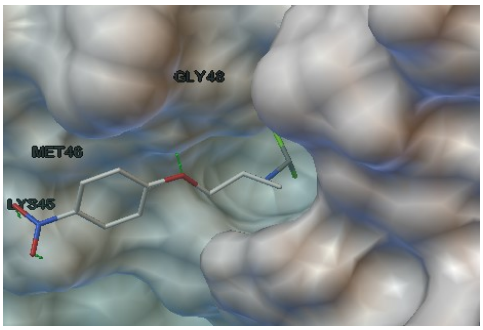



Conformer-9

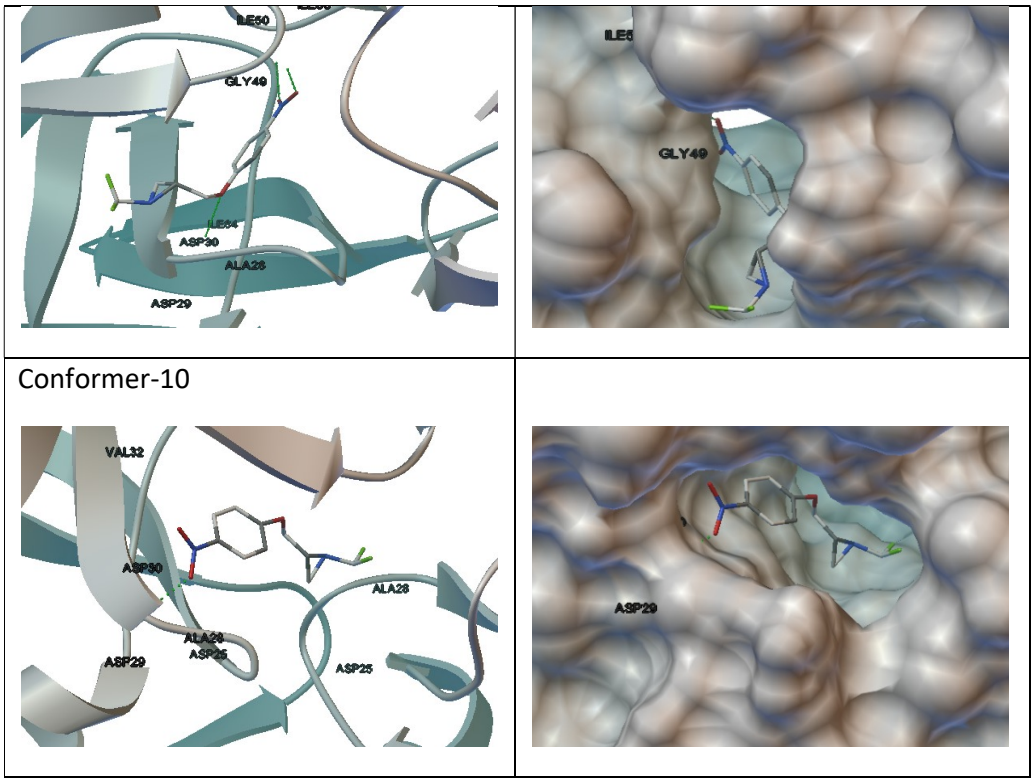
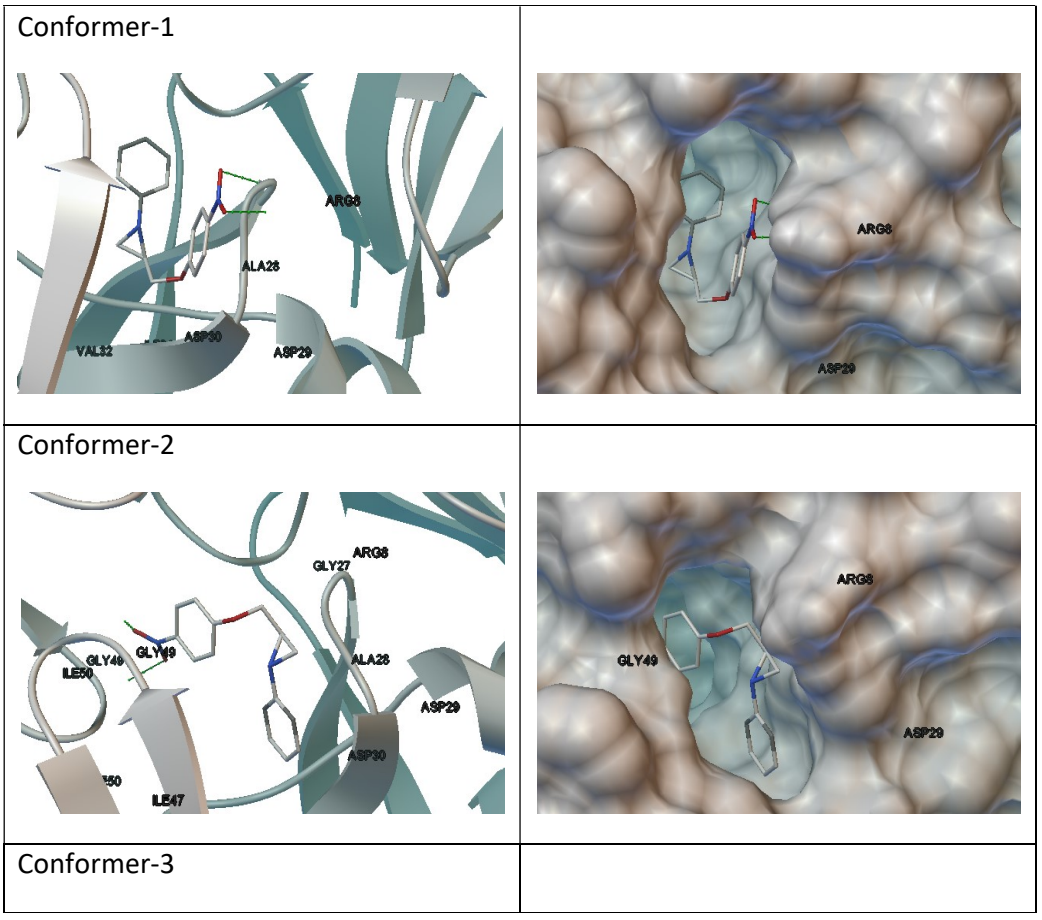



**Fig. S4** Molecular docking interaction of Inhibitor-4 with HIV-1 Protease.



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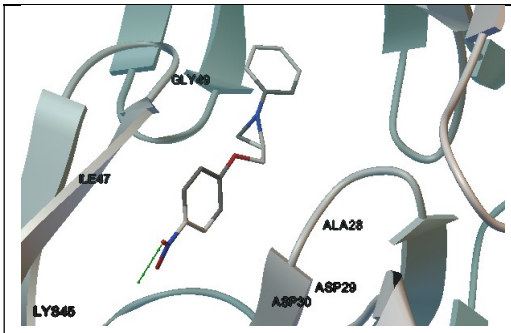
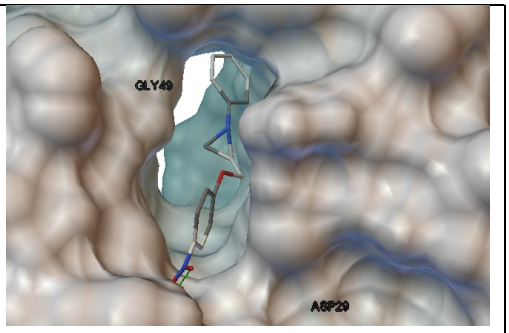
<tr><td> 
</td><td> 
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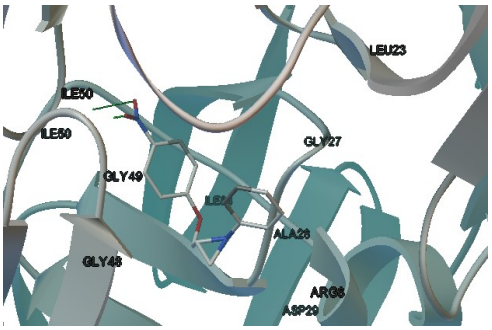
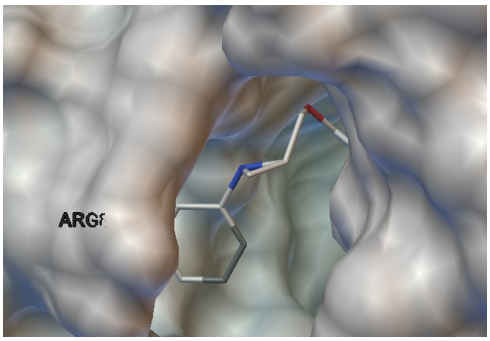
<tr><td> 
</td><td> 
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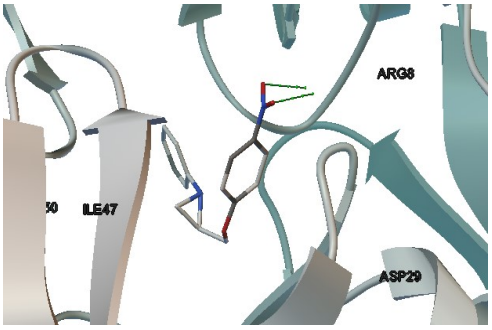
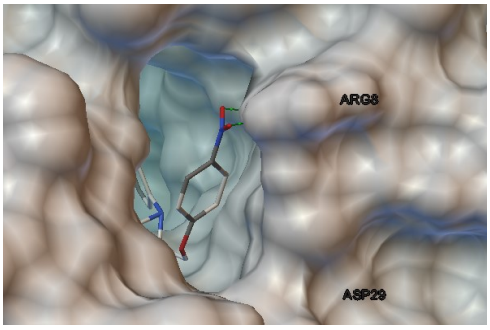
<tr><td> 
</td><td> 
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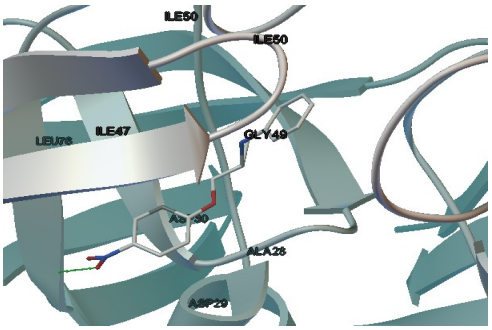
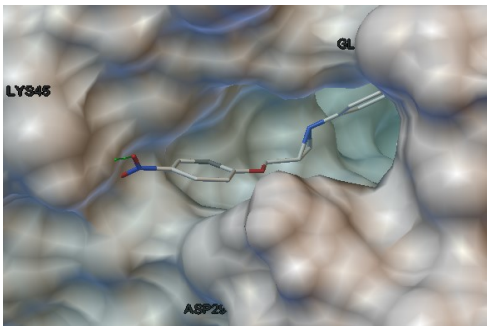
<tr><td> 
</td><td> 
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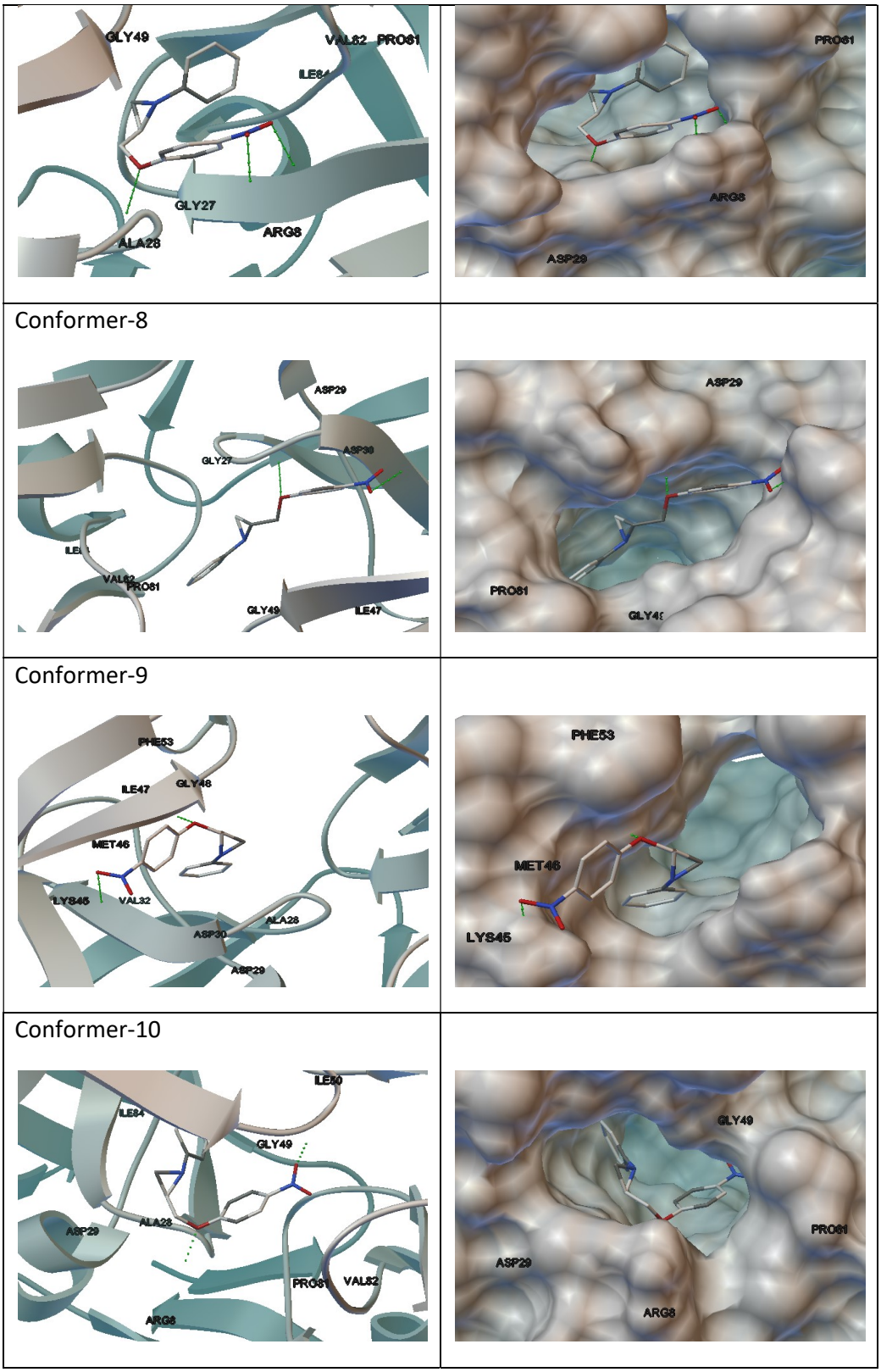


**Fig. S5** Molecular docking interaction of Inhibitor-5 with HIV-1 Protease.

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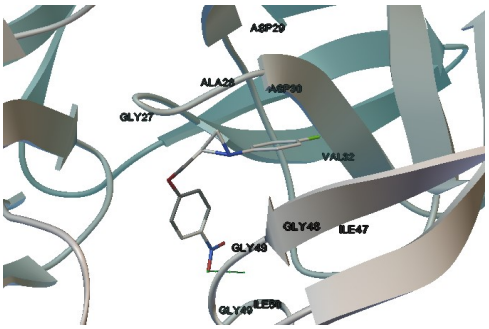
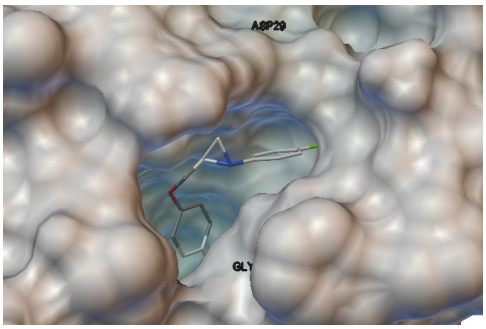
|  |  |
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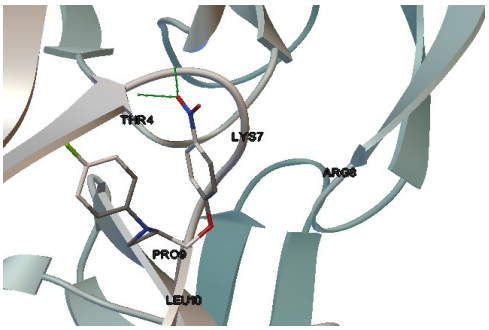
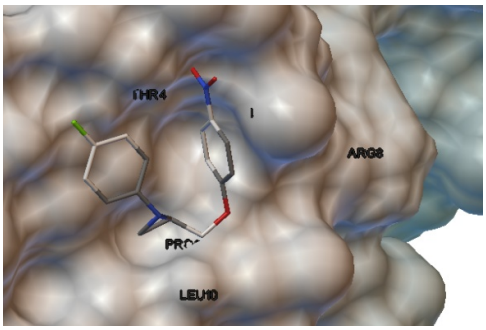
|  |  |
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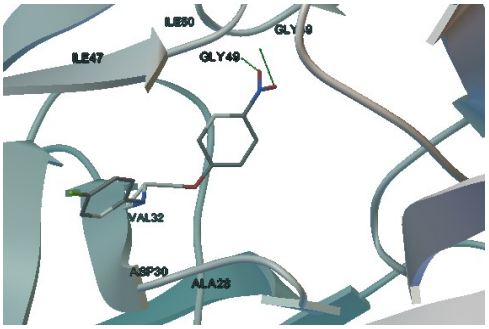
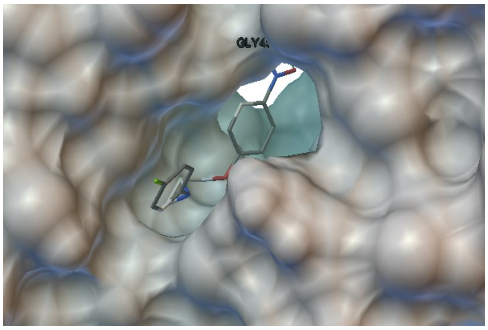
|  |  |
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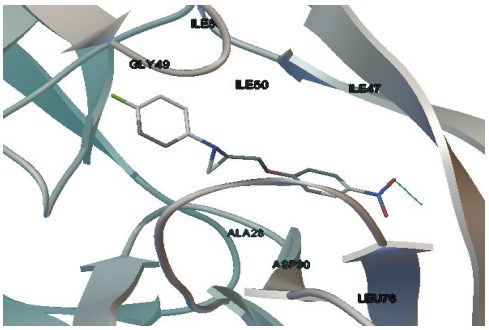
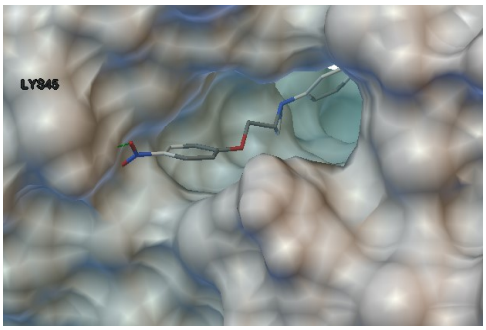
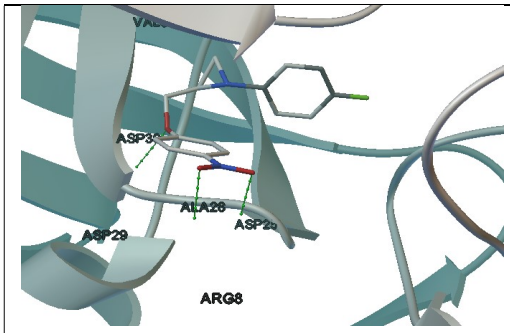
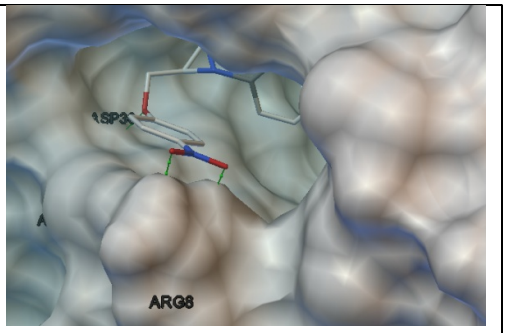
|  |  |
| Conformer-5 | |

| | |
|---|---|
|  |  |
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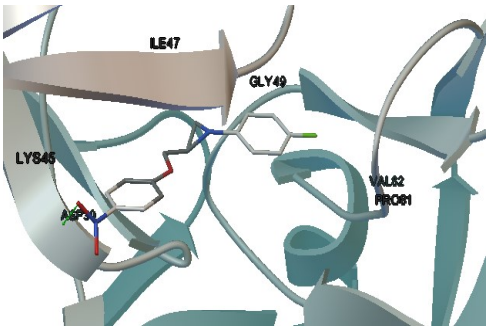
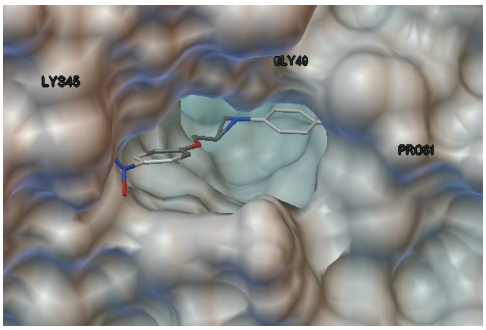
|  |  |
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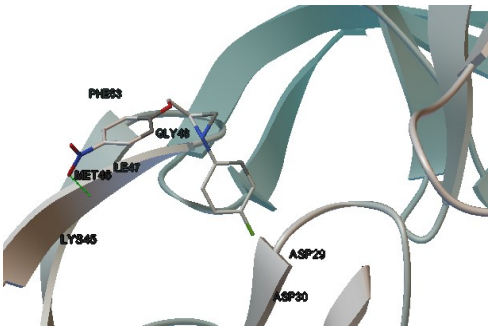
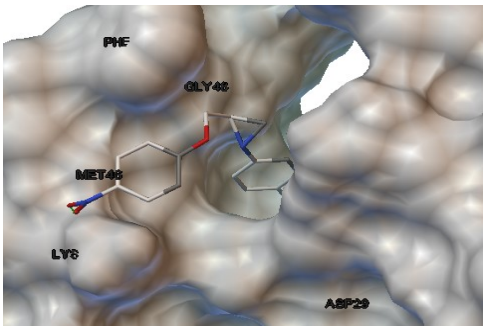
|  |  |
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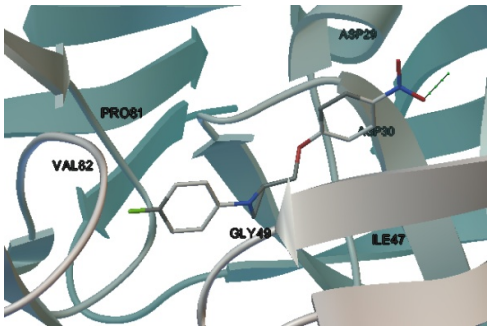
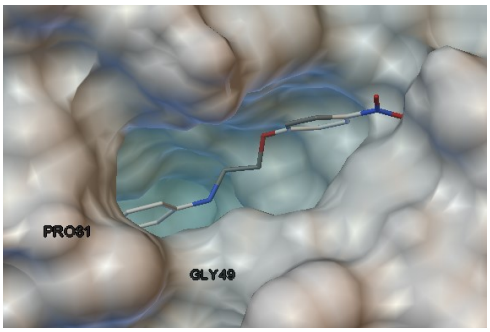
|  |  |
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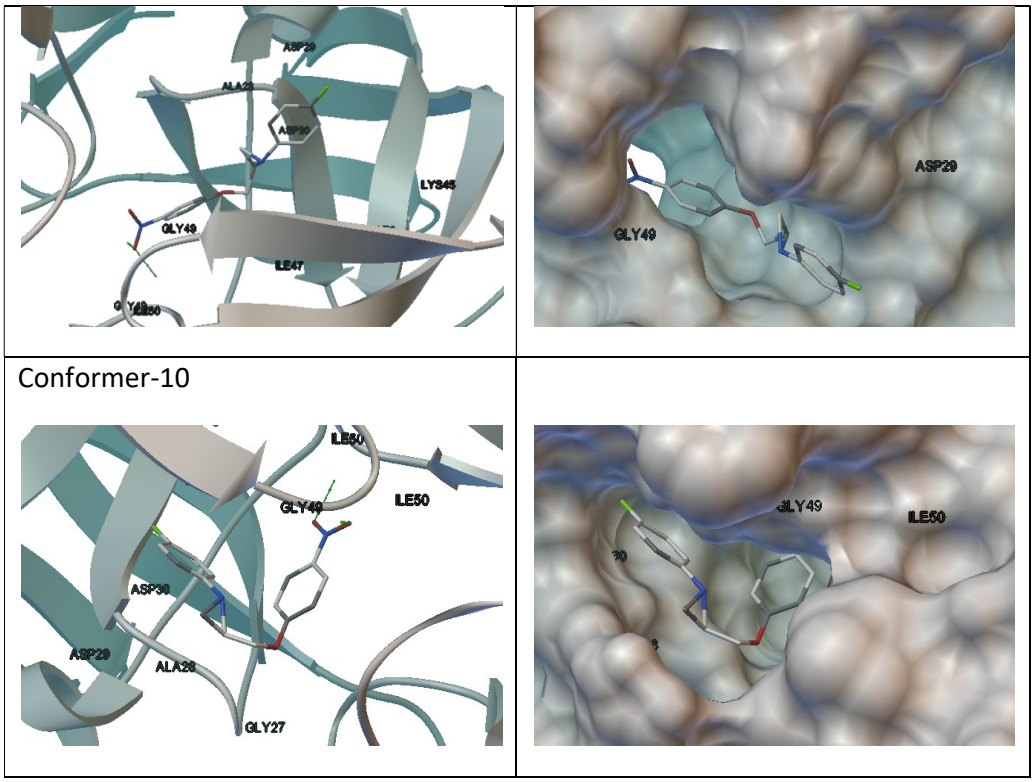



**Fig. S6** Molecular docking interaction of Inhibitor-6 with HIV-1 Protease.

**Table S7.1** Conformations of Inhibitor-1 and its binding affinity to HIV-1 in kcal/mol.

| Inhibitor | Conformation number | H-Bond involving Residues | H-Bond Distance (Å) | Binding Energy (Kcal/mol) | Average Binding Energy (Kcal/mol) |
|---|---|---|---|---|---|
| Inhibitor-1 | 1 | ARG8:HH12 | 2.094 | -4.826 | -5.55 |
| | | ILE50:HN | 2.065 | -0.277 | |
| | | GLY27:H | 1.843 | -0.034 | |
| | 2 | ASP30:HN | 1.925 | -4.458 | -5.13 |
| | | GLY27:H | 1.943 | -0.08 | |
| | 3 | ASP29:HN | 1.976 | -5.912 | -5.99 |
| | | ASP30:HN | 2.06 | -5.343 | |
| | | ASP25:HN | 1.925 | -0.001 | |
| | 4 | ILE50:HN | 1.772 | -0.409 | -5.62 |
| | | ILE50:HN | 2.047 | -5.102 | |
| | | ASP25:HN | 1.937 | -0.076 | |
| | 5 | ASP30:HN | 2.03 | -5.816 | -5.72 |
| | | GLY27:H | 1.739 | -0.14 | |
| | 6 | ILE50:HN | 1.769 | -6.912 | -5.83 |
| | | ILE50:HN | 2.239 | -3.525 | |
| | | ASP25:HN | 1.813 | -0.053 | |
| | 7 | ASP29:HN | 1.875 | -6.256 | **-6.37** |
| | | ASP30:HN | 2.112 | -4.657 | |
| | | GLY27:H | 2.05 | -0.27 | |
| | 8 | ASP30:HN | 1.854 | -5.09 | -6.02 |

| | | | | | |
|---|---|---|---|---|---|
| | | ASP25:HN | 2.176 | -0.095 | |
| | 9 | ARG8:HH12 | 1.859 | -6.751 | -5.62 |
| | | ASN83:HN | 1.705 | -0.064 | |
| | 10 | ASP29:HN | 2.025 | -5.112 | -6.18 |
| | | ASP30:HN | 2.105 | -5.216 | |
| | | GLY27:H | 1.842 | -0.443 | |

**Table S7.2** Conformations of Inhibitor-2 and its binding affinity to HIV-1 in kcal/mol.

| Inhibitor | Conformation | H-Bond involving Residues | H-Bond Distance(Å) | Binding Energy (Kcal/mol) | Average Binding Energy (Kcal/mol) |
|---|---|---|---|---|---|
| Inhibitor -2 | 1 | ASP30:HN | 1.746 | -3.559 | **-5.21** |
| | 2 | ASP29:HN | 1.944 | -4.464 | -5.0 |
| | | ADP30:HN | 2.057 | -4.878 | |
| | 3 | ILE50:HN | 1.82 | -7.116 | -5.4 |
| | | ILE50:HN | 1.844 | -6.283 | |
| | 4 | ASP30:HN | 1.894 | -5.05 | -5.05 |
| | 5 | TRP6:HN | 2.11 | -0.255 | -4.54 |
| | | LYS7:HN | 2.201 | -3.798 | |
| | 6 | ARG8:HH12 | 2.202 | -4.7 | -4.7 |
| | 7 | ASP29:HN | 1.937 | -6.435 | -4.89 |
| | | ASP30:HN | 2.07 | -5.20 | |
| | 8 | ARG: HH12 | 2.034 | -5.187 | -5.05 |
| | | ILE50:HN | 2.248 | -3.576 | |
| | 9 | ARG8:HH12 | 1.923 | -6.463 | -5.0 |
| | | ILE50:HN | 2.152 | -4.692 | |
| | 10 | ILE50:HN | 1.785 | -6.6 | -4.91 |
| | | ILE50:HN | 1.954 | -6.145 | |

**Table S7.3** Conformations of Inhibitor-3 and its binding affinity to HIV-1 in kcal/mol.

| Inhibitor | Conformation | H-Bond involving Residues | H-Bond Distance(Å) | Binding Energy (Kcal/mol) | Average Binding Energy (Kcal/mol) |
|---|---|---|---|---|---|
| Inhibitor-3 | 1 | ILE50:HN | 1.807 | -7.555 | -4.63 |
| | | ILE50:HN | 1.913 | -6.776 | |
| | 2 | THR4:HG1 | 1.786 | -0.692 | -4.60 |
| | | TRP6:HN | 1.899 | -0.501 | |
| | 3 | LYS45:HZ2 | 1.698 | -0.998 | -4.65 |
| | 4 | ASP30:HN | 2.02 | -3.125 | -4.64 |
| | 5 | LYS20:HZ2 | 1.738 | 0.0 | -4.66 |
| | | ASN83:HD21 | 2.008 | -3.953 | |
| | 6 | THR: HG1 | 1.957 | -3.35 | -4.15 |
| | | TRP6:HN | 2.168 | -0.224 | |
| | | LYS7:HN | 2.193 | -3.532 | |
| | 7 | LYS45:HZ2 | 1.683 | -0.988 | **-4.67** |
| | 8 | ASP29:HN | 2.008 | -4.765 | -4.55 |
| | | LYS45:HZ2 | 1.756 | -0.015 | |

| | | | | | |
|---|---|---|---|---|---|
| | 9 | ARG8:HH12 | 1.955 | -4.486 | -4.3 |
| | | ILE50:HN | 2.026 | -0.609 | |
| | 10 | LYS20:HZ2 | 1.853 | -5.637 | -4.05 |
| | | GLU21:HN | 2.081 | -0.77 | |
| | | ASN83:HD21 | 2.076 | -3.032 | |

**Table S7.4** Conformations of Inhibitor-4 and its binding affinity to HIV-1 in kcal/mol.

| Inhibitor | Conformation number | H-Bond involving Residues | H-Bond Distance(Å) | Binding Energy (Kcal/mol) | Average Binding Energy (Kcal/mol) |
|---|---|---|---|---|---|
| Inhibitor- 4 | 1 | LYS45:HZ2 | 1.681 | -0.767 | -4.67 |
| | 2 | ASP30:HN | 1.844 | -5.404 | -4.43 |
| | 3 | LYS45:HZ1 | 1.995 | -0.098 | -4.94 |
| | | LYS45:HZ3 | 1.839 | -0.005 | |
| | | GLY48:HN | 2.205 | -4.156 | |
| | 4 | LYS45:HZ1 | 1.71 | -0.172 | -4.72 |
| | | GLY48:HN | 2.124 | -3.567 | |
| | 5 | LYS45:HZ1 | 1.88 | -0.017 | **-5.37** |
| | | LYS45:HZ3 | 1.956 | -0.006 | |
| | | GLY48:HN | 2.008 | -5.523 | |
| | 6 | LYS45:HZ2 | 1.668 | -0.969 | -4.4 |
| | 7 | LYS45:HZ1 | 1.787 | -1.569 | -5.07 |
| | | GLY48:HN | 2.1 | -5.053 | |
| | 8 | LYS45:HZ1 | 2.124 | -0.007 | -5.0 |
| | | LYS45:HZ3 | 2.104 | -0.115 | |
| | | GLY48:HN | 2.093 | -4.639 | |
| | 9 | ASP29:HN | 2.222 | -2.676 | -5.09 |
| | | ILE50:HN | 1.852 | -6.474 | |
| | | ILE50:HN | 1.993 | -5.357 | |
| | 10 | ASP29:HN | 1.925 | -5.637 | -4.61 |
| | | ASP30:HN | 1.928 | -6.665 | |

**Table S7.5** Conformations of Inhibitor-5 and its binding affinity to HIV-1 in kcal/mol.

| Inhibitor | Conformation | H-Bond involving Residues | H-Bond Distance(Å) | Binding Energy (Kcal/mol) | Average Binding Energy (Kcal/mol) |
|---|---|---|---|---|---|
| Inhibitor-5 | 1 | ARG8:HH12 | 1.888 | -5.489 | -5.95 |
| | | ARG8:HH22 | 1.845 | -7.773 | |
| | 2 | ILE50:HN | 2.026 | -2.274 | -5.32 |
| | | ILE50:HN | 2.03 | -1.637 | |
| | 3 | LYS45:HZ2 | 2.06 | -5.7 | -5.7 |
| | 4 | ILE50:HN | 1.684 | -5.963 | **-6.37** |
| | | ILE50:HN | 2.104 | -5.167 | |
| | 5 | ARG8:HH12 | 1.857 | -6.007 | -5.63 |
| | | ARG8:HH22 | 1.723 | -7.683 | |
| | 6 | LYS45:HZ2 | 2.063 | -6.18 | -6.18 |
| | 7 | ASP29:HN | 2.131 | -4.14 | -5.3 |
| | | ARG8:HH12 | 2.071 | -0.546 | |
| | | ARG8:HH22 | 2.034 | -4.154 | |

| | | | | | |
|---|---|---|---|---|---|
| | 8 | ASP29:HN | 2.203 | -4.176 | -6.33 |
| | | LYS45:HZ2 | 1.988 | -0.12 | |
| | 9 | LYS45:HZ3 | 1.899 | -0.322 | -6.33 |
| | | GLY48:HN | 0.322 | -0.963 | |
| | 10 | ARG8:HH12 | 1.934 | -2.828 | -5.01 |
| | | ILE50:HN | 1.767 | -0.26 | |

**Table S7.6** Conformations of Inhibitor-6 and its binding affinity to HIV-1 in kcal/mol.

| Inhibitor | Conformation | H-Bond involving Residues | H-Bond Distance(Å) | Binding Energy (Kcal/mol) | Average Binding Energy (Kcal/mol) |
|---|---|---|---|---|---|
| Inhibitor-6 | 1 | ILE50:HN | 1.981 | 6.218 | -5.83 |
| | | ILE50:HN | 2.091 | -1.215 | |
| | 2 | THR4:HG1 | 1.793 | -0.376 | -5.43 |
| | | THR6:HN | 1.892 | -0.466 | |
| | 3 | ILE50:HN1 | 1.682 | -6.251 | -5.83 |
| | | ILE50:HN1 | 1.851 | -6.562 | |
| | 4 | LYS45:HZ2 | 1.924 | -0.128 | -5.98 |
| | 5 | ARG8:HH12 | 1.862 | -5.672 | -5.80 |
| | | ARG8:HH22 | 1.991 | -6.448 | |
| | | ASP30:HN | 2.179 | -4.138 | |
| | 6 | LYS45:HZ2 | 1.673 | -0.607 | -5.70 |
| | 7 | LYS45:HZ3 | 1.79 | -0.309 | -5.18 |
| | **8** | LYS45:HZ2 | 1.667 | -0.277 | **-6.13** |
| | 9 | ILE50:HN | 1.909 | -5.954 | -5.71 |
| | | ILE50:HN | 2.078 | -1.684 | |
| | 10 | ILE50:HN | 1.906 | -6.987 | -5.93 |
| | | ILE50:HN | 1.946 | -6.333 | |

**Table S8.1** Clustering Histogram for all the 10 different conformations of Inhibitor-1 bound to HIV-1.

| Cluster rank | Sub rank | Conformation number | Binding Energy (kcal/mol) | Mean Binding Energy (kcal/mol) | Cluster RMSD |
|---|---|---|---|---|---|
| 1 | 1 | 7 | -6.37 | -6.37 | 0.00 |
| 2 | 1 | 10 | -6.18 | -5.92 | 0.00 |
| | 2 | 8 | -6.02 | | 1.28 |
| | 3 | 3 | -5.99 | | 0.94 |
| | 4 | 2 | -5.73 | | 1.30 |
| | 5 | 5 | -5.72 | | 1.30 |
| 3 | 1 | 6 | -5.83 | -5.72 | 0.00 |
| | 2 | 4 | -5.62 | | 1.43 |
| 4 | 1 | 9 | -5.62 | -5.58 | 0.00 |
| | 2 | 1 | -5.55 | | 1.49 |

**Table S8.2** Clustering Histogram for all the 10 different conformations of Inhibitor-2 bound to HIV-1.

| Cluster rank | Sub rank | Conformation number | Binding energy (kcal/mol) | Mean binding energy (kcal/mol) | Cluster RMSD |
|---|---|---|---|---|---|
| 1 | 1 | 3 | -5.40 | -5.15 | 0.00 |
| | 2 | 10 | -4.91 | | 1.43 |
| 2 | 1 | 1 | -5.21 | -5.05 | 0.00 |
| | 2 | 4 | -5.05 | | 0.76 |
| | 3 | 7 | -4.89 | | 1.60 |
| 3 | 1 | 8 | -5.05 | -4.91 | 0.00 |
| | 2 | 9 | -5.00 | | 0.48 |
| | 3 | 6 | -4.7 | | 1.93 |
| 4 | 1 | 2 | -5.00 | -5.00 | 0.00 |
| 5 | 1 | 5 | -4.54 | -4.54 | 0.00 |

**Table S8.3** Clustering Histogram for all the 10 different conformations of Inhibitor-3 bound to HIV-1.

| Cluster rank | Sub rank | Conformation number | Binding energy (kcal/mol) | Mean binding energy (kcal/mol) | Cluster RMSD |
|---|---|---|---|---|---|
| 1 | 1 | 7 | -4.67 | -4.66 | 0.00 |
| | 2 | 3 | -4.65 | | 0.40 |
| 2 | 1 | 5 | -4.66 | -4.66 | 0.00 |
| 3 | 1 | 4 | -4.64 | -4.64 | 0.00 |
| 4 | 1 | 1 | -4.63 | -4.63 | 0.00 |
| 5 | 1 | 2 | -4.60 | -4.60 | 0.00 |
| 6 | 1 | 8 | -4.55 | -4.55 | 0.00 |
| 7 | 1 | 9 | -4.30 | -4.30 | 0.00 |
| 8 | 1 | 6 | -4.15 | -4.15 | 0.00 |
| 9 | 1 | 10 | -4.05 | -4.05 | 0.00 |

**Table S8.4** Clustering Histogram for all the 10 different conformations of Inhibitor-4 bound to HIV-1.

| Cluster rank | Sub rank | Conformation number | Binding energy (kcal/mol) | Mean binding energy (kcal/mol) | Cluster RMSD |
|---|---|---|---|---|---|
| 1 | 1 | 5 | -5.37 | -5.02 | 0.00 |
| | 2 | 7 | -5.07 | | 1.10 |
| | 3 | 8 | -5.00 | | 0.83 |
| | 4 | 3 | -4.94 | | 0.49 |
| | 5 | 4 | -4.72 | | 1.76 |
| 2 | 1 | 9 | -5.09 | -5.09 | 0.00 |
| 3 | 1 | 1 | -4.67 | -4.53 | 0.00 |
| | 2 | 6 | -4.40 | | 1.07 |
| 4 | 1 | 10 | -4.61 | -4.61 | 0.00 |
| 5 | 1 | 2 | -4.43 | -4.43 | 0.00 |

**Table S8.5** Clustering Histogram for all the 10 different conformations of Inhibitor-5 bound to HIV-1.

| Cluster rank | Sub rank | Conformation number | Binding energy (kcal/mol) | Mean binding energy (kcal/mol) | Cluster RMSD |
|---|---|---|---|---|---|
| 1 | 1 | 7 | -6.37 | -6.37 | 0.00 |
| 2 | 1 | 10 | -6.18 | -5.92 | 0.00 |
| | 2 | 8 | -6.02 | | 1.28 |
| | 3 | 3 | -5.99 | | 0.94 |
| | 4 | 2 | -5.73 | | 1.30 |
| | 5 | 5 | -5.72 | | 1.30 |
| 3 | 1 | 6 | -5.83 | -5.72 | 0.00 |
| | 2 | 4 | -5.62 | | 1.43 |
| 4 | 1 | 9 | -5.62 | -5.58 | 0.00 |
| | 2 | 1 | -5.55 | | 1.49 |

**Table S8.6** Clustering Histogram for all the 10 different conformations of Inhibitor-6 bound to HIV-1.

| Cluster rank | Sub rank | Conformation number | Binding energy (kcal/mol) | Mean binding energy (kcal/mol) | Cluster RMSD |
|---|---|---|---|---|---|
| 1 | 1 | 8 | -6.13 | -5.91 | 0.00 |
| | 2 | 6 | -5.70 | | 0.48 |
| 2 | 1 | 4 | -5.98 | -5.98 | 0.00 |
| 3 | 1 | 10 | -5.93 | -5.88 | 0.00 |
| | 2 | 1 | -5.83 | | 0.70 |
| 4 | 1 | 3 | -5.83 | -5.77 | 0.00 |
| | 2 | 9 | -5.71 | | 1.11 |
| 5 | 1 | 5 | -5.80 | -5.80 | 0.00 |
| 6 | 1 | 2 | -5.43 | -5.43 | 0.00 |
| 7 | 1 | 7 | -5.18 | -5.18 | 0.00 |

**Table S9.1** Covalent docking conformations of Inhibitor-1 and its binding affinity to HIV-1 in kcal/mol.

| Inhibitor | Conformation number | Binding Energy (kcal/mol) | Mean Binding Energy (kcal/mol) |
|---|---|---|---|
| **Inhibitor-1** | 1 | -6.62 | **-6.62** |
| | 2 | -6.66 | |
| | 3 | -6.66 | |
| | 4 | -6.56 | |
| | 5 | -6.52 | |
| | 6 | -6.59 | |
| | 7 | -6.60 | |
| | 8 | -6.66 | |
| | 9 | **-6.70** | |
| | 10 | -6.58 | |

**Table S9.2** Covalent docking conformations of Inhibitor-2 and its binding affinity to HIV-1 in kcal/mol.

| Inhibitor | Conformation number | Binding Energy (kcal/mol) | Mean Binding Energy (kcal/mol) |
|---|---|---|---|
| Inhibitor-2 | 1 | **-6.45** | **-6.38** |
| | 2 | -6.43 | |
| | 3 | -6.42 | |
| | 4 | -6.42 | |
| | 5 | -6.32 | |
| | 6 | -6.44 | |
| | 7 | -6.42 | |
| | 8 | -6.21 | |
| | 9 | -6.40 | |
| | 10 | -6.33 | |

**Table S9.3** Covalent docking conformations of Inhibitor-3 and its binding affinity to HIV-1 in kcal/mol.

| Inhibitor | Conformation number | Binding Energy (kcal/mol) | Mean Binding Energy (kcal/mol) |
|---|---|---|---|
| Inhibitor-3 | 1 | -5.75 | **-5.72** |
| | 2 | -5.71 | |
| | 3 | -5.85 | |
| | 4 | **-5.93** | |
| | 5 | -5.67 | |
| | 6 | -5.76 | |
| | 7 | -5.65 | |
| | 8 | -5.58 | |
| | 9 | -5.76 | |
| | 10 | -5.55 | |

**Table S9.4** Covalent docking conformations of Inhibitor- 4 and its binding affinity to HIV-1 in kcal/mol.

| Inhibitor | Conformation number | Binding Energy (kcal/mol) | Mean Binding Energy (kcal/mol) |
|---|---|---|---|
| Inhibitor-4 | 1 | -5.97 | **-6.07** |
| | 2 | -6.02 | |
| | 3 | -6.09 | |
| | 4 | -6.27 | |
| | 5 | -6.08 | |
| | 6 | **-6.28** | |
| | 7 | -6.01 | |
| | 8 | -6.01 | |
| | 9 | -6.01 | |
| | 10 | -6.00 | |

**Table S9.5** Covalent docking conformations of Inhibitor- 5 and its binding affinity to HIV-1 in kcal/mol.

| Inhibitor | Conformation number | Binding Energy (kcal/mol) | Mean Binding Energy (kcal/mol) |
|---|---|---|---|
| Inhibitor-5 | 1 | -7.56 | -7.52 |
| | 2 | -7.51 | |
| | 3 | -7.46 | |
| | 4 | -7.56 | |
| | 5 | -7.41 | |
| | 6 | -7.56 | |
| | 7 | -7.53 | |
| | 8 | -7.55 | |
| | 9 | **-7.57** | |
| | 10 | -7.53 | |

**Table S9.6** Covalent docking conformations of Inhibitor- 6 and its binding affinity to HIV-1 in kcal/mol.

| Inhibitor | Conformation number | Binding Energy (kcal/mol) | Mean Binding Energy (kcal/mol) |
|---|---|---|---|
| Inhibitor-6 | 1 | -7.44 | -7.38 |
| | 2 | -7.44 | |
| | 3 | -7.33 | |
| | 4 | -7.35 | |
| | 5 | **-7.45** | |
| | 6 | -7.22 | |
| | 7 | -7.33 | |
| | 8 | -7.41 | |
| | 9 | -7.36 | |
| | 10 | -7.43 | |

**Table S10** Distance between the catalytic dyads Asp25 / Asp25' for different X-ray structures and simulated 2SYH structure.

| X-Ray Structures | CG - CG | CB - CB |
|---|---|---|
| Overlaid structure 2SYH | 5.02Å | 7.17Å |
| 1YTH | 5.02Å | 7.17Å |
| 1AID | 5.10Å | 7.06Å |
| 2AID | 4.70Å | 7.36Å |
| 1D4K | 4.99Å | 7.39Å |
| 1D4L | 4.97Å | 7.35Å |
| 1EBW | 4.98Å | 7.39Å |
| 1EBY | 4.91Å | 7.33Å |
| 1ZSF | 4.81Å | 7.22Å |
| 3AID | 5.24Å | 7.47Å |

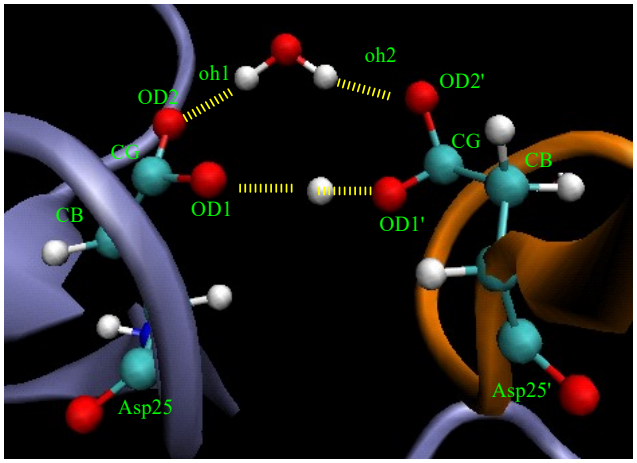
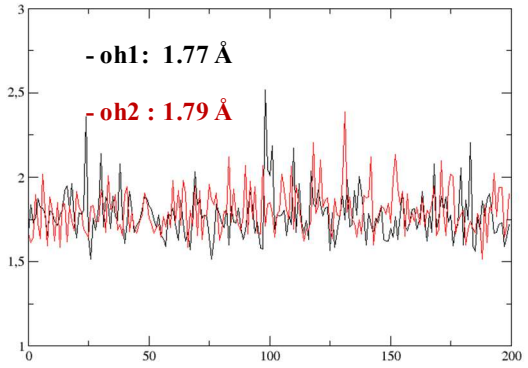
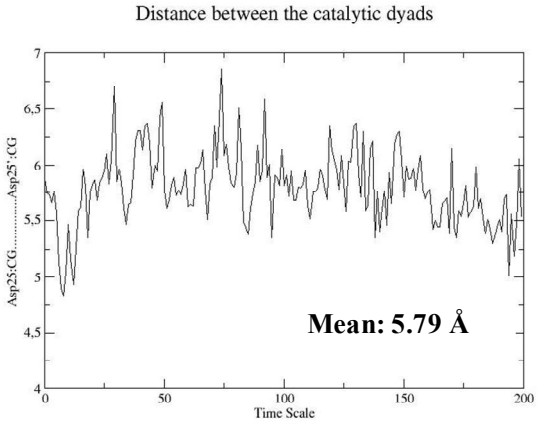



**Fig. S7** Scheme of the active site of HIV-1 PR (2SYH) together with the denotation of the important atomic centers.

(a)




(b)



(c)

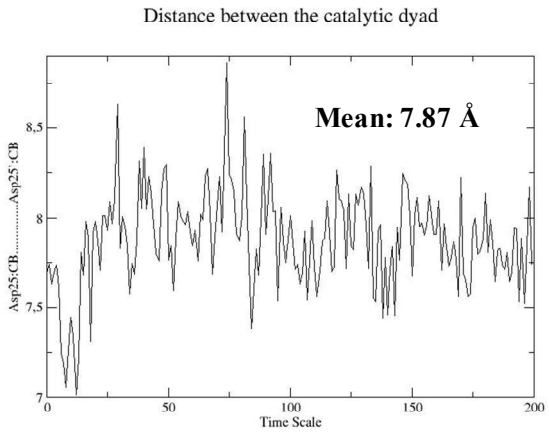



**Fig. S8** Time evolution of distances plotted as a function of simulation time (ps): (a) water molecule hydrogen bonded to both Oδ2 atoms via oh1 and oh2, (b) CB-CB' distance between the catalytic dyads Asp25 / Asp25' and (c)CG-CG' distance. The computations were performed for the free enzyme obtained from the overlaid 2SYH structure.

**Table S11** Cartesian coordinates of the QM part for R, TS and P structures obtained for the inhibition process of the inhibitor-1 (AZNP).

| | R | | | TS | | | P | | |
|---|---|---|---|---|---|---|---|---|---|
| Atom | X | Y | Z | X | Y | Z | X | Y | Z |
| N | -1.695 | 0.578 | 3.073 | -1.784 | 0.760 | 3.170 | -1.719 | 0.644 | 3.226 |
| H | -2.581 | 0.800 | 2.649 | -2.675 | 1.031 | 2.787 | -2.603 | 0.902 | 2.816 |
| C | -0.548 | 0.674 | 2.198 | -0.676 | 0.828 | 2.249 | -0.588 | 0.643 | 2.331 |
| H | 0.238 | 0.033 | 2.578 | 0.097 | 0.139 | 2.572 | 0.199 | 0.026 | 2.748 |
| C | -0.877 | 0.186 | 0.755 | -1.123 | 0.404 | 0.821 | -0.995 | 0.028 | 0.963 |
| H | -1.482 | -0.721 | 0.871 | -1.826 | -0.425 | 0.963 | -1.585 | -0.860 | 1.210 |
| H | -1.509 | 0.957 | 0.292 | -1.671 | 1.248 | 0.382 | -1.643 | 0.759 | 0.462 |
| C | 0.325 | -0.124 | -0.182 | 0.002 | -0.044 | -0.135 | 0.148 | -0.343 | 0.030 |
| O | 1.288 | 0.724 | -0.225 | 1.003 | 0.727 | -0.310 | 0.923 | 0.464 | -0.474 |
| O | 0.272 | -1.181 | -0.879 | -0.154 | -1.175 | -0.707 | 0.162 | -1.674 | -0.212 |
| C | -0.000 | 2.093 | 2.170 | -0.062 | 2.217 | 2.203 | -0.017 | 2.041 | 2.157 |
| O | -0.685 | 3.064 | 1.845 | -0.711 | 3.217 | 1.896 | -0.684 | 2.971 | 1.709 |
| N | 7.015 | 0.620 | 2.284 | 6.985 | 0.573 | 2.221 | 6.980 | 0.584 | 2.216 |
| H | 7.903 | 0.424 | 2.718 | 7.864 | 0.367 | 2.666 | 7.868 | 0.363 | 2.635 |
| C | 6.074 | -0.495 | 2.247 | 6.021 | -0.524 | 2.179 | 6.007 | -0.506 | 2.183 |
| H | 5.213 | -0.206 | 1.651 | 5.158 | -0.214 | 1.595 | 5.152 | -0.200 | 1.587 |
| C | 6.701 | -1.808 | 1.659 | 6.610 | -1.840 | 1.556 | 6.588 | -1.834 | 1.588 |
| H | 7.574 | -1.497 | 1.083 | 7.433 | -1.527 | 0.912 | 7.438 | -1.533 | 0.973 |
| H | 7.057 | -2.464 | 2.466 | 7.038 | -2.464 | 2.353 | 6.978 | -2.470 | 2.396 |
| C | 5.722 | -2.582 | 0.734 | 5.589 | -2.669 | 0.722 | 5.580 | -2.644 | 0.703 |
| O | 4.729 | -3.186 | 1.264 | 4.663 | -3.291 | 1.346 | 4.651 | -3.296 | 1.313 |
| O | 5.956 | -2.543 | -0.519 | 5.724 | -2.674 | -0.545 | 5.745 | -2.603 | -0.546 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| C | 5.535 | -0.851 | 3.626 | 5.505 | -0.867 | 3.573 | 5.477 | -0.833 | 3.572 |
| O | 6.074 | -0.450 | 4.655 | 6.075 | -0.471 | 4.587 | 5.988 | -0.365 | 4.589 |
| N | 3.941 | -1.850 | -2.047 | 3.417 | -2.233 | -1.803 | 3.324 | -2.479 | -2.238 |
| C | 3.205 | -0.767 | -1.293 | 2.715 | -1.506 | -0.681 | 2.533 | -1.975 | -1.077 |
| C | 2.495 | -1.997 | -1.682 | 1.742 | -2.196 | -1.516 | 1.029 | -2.259 | -1.282 |
| H | 2.991 | 0.138 | -1.845 | 2.700 | -0.420 | -0.714 | 2.672 | -0.901 | -0.934 |
| H | 3.552 | -0.634 | -0.275 | 2.959 | -1.961 | 0.278 | 2.880 | -2.490 | -0.176 |
| H | 1.833 | -1.913 | -2.539 | 1.321 | -1.658 | -2.356 | 0.680 | -1.817 | -2.228 |
| H | 4.163 | -1.672 | -3.044 | 3.743 | -1.591 | -2.528 | 3.483 | -1.709 | -2.894 |
| H | 4.722 | -2.333 | -1.463 | 4.226 | -2.800 | -1.387 | 4.253 | -2.718 | -1.843 |
| C | 2.216 | -3.173 | -0.770 | 1.133 | -3.553 | -1.203 | 0.672 | -3.753 | -1.287 |
| H | 1.142 | -3.235 | -0.587 | 0.903 | -4.106 | -2.127 | 0.894 | -4.180 | -2.272 |
| H | 2.796 | -3.121 | 0.159 | 0.206 | -3.372 | -0.645 | -0.398 | -3.878 | -1.072 |
| O | 2.701 | -4.363 | -1.527 | 2.100 | -4.276 | -0.414 | 1.481 | -4.405 | -0.280 |
| C | 1.787 | -7.493 | 0.243 | 1.147 | -7.865 | -0.441 | 0.969 | -8.070 | -0.485 |
| H | 0.939 | -8.002 | 0.697 | 0.304 | -8.536 | -0.584 | 0.202 | -8.820 | -0.662 |
| C | 4.141 | -7.537 | -0.434 | 3.516 | -7.560 | 0.089 | 3.278 | -7.532 | 0.119 |
| H | 5.074 | -8.088 | -0.508 | 4.481 | -8.005 | 0.312 | 4.280 | -7.879 | 0.355 |
| C | 3.017 | -8.157 | 0.132 | 2.406 | -8.391 | -0.129 | 2.265 | -8.470 | -0.139 |
| C | 4.017 | -6.247 | -0.937 | 3.368 | -6.188 | -0.026 | 2.989 | -6.175 | 0.031 |
| H | 4.863 | -5.732 | -1.387 | 4.191 | -5.494 | 0.136 | 3.739 | -5.405 | 0.226 |
| C | 2.779 | -5.580 | -0.877 | 2.107 | -5.639 | -0.350 | 1.683 | -5.757 | -0.306 |
| C | 1.672 | -6.189 | -0.250 | 0.990 | -6.478 | -0.551 | 0.676 | -6.706 | -0.580 |
| H | 0.720 | -5.665 | -0.180 | 0.006 | -6.061 | -0.757 | -0.336 | -6.385 | -0.818 |
| N | 3.109 | -9.577 | 0.514 | 2.621 | -9.849 | -0.110 | 2.606 | -9.905 | -0.110 |
| O | 2.063 | -10.218 | 0.711 | 1.737 | -10.604 | -0.551 | 1.790 | -10.732 | -0.557 |
| O | 4.258 | -10.084 | 0.595 | 3.707 | -10.240 | 0.381 | 3.710 | -10.211 | 0.401 |