

## Newly Synthesized Series of Oxindole-Oxadiazole Conjugates as Potential Anti-SARS-CoV-2 Agents: *In Silico* and *In Vitro* Studies

Rana M. El-Masry<sup>a</sup>, Ahmed A. Al Karmalawy<sup>b\*</sup>, Radwan Alnajjar<sup>c,d</sup>, Sara H. Mahmoud<sup>e</sup>, Ahmed Mostafa<sup>e</sup>, Hanan H. Kadry<sup>f</sup>, Sahar M. Abou-Seri<sup>g\*</sup>, Azza T. Taher<sup>f,h\*</sup>

<sup>a</sup> Organic Chemistry Department, Faculty of Pharmacy, October University for Modern Sciences and Arts (MSA), October 6 city, Giza, Egypt

<sup>b</sup> Department of Pharmaceutical Medicinal Chemistry, Faculty of Pharmacy, Horus University-Egypt, New Damietta 34518, Egypt.

<sup>c</sup> Department of Chemistry, Faculty of Science, University of Benghazi, Benghazi, Libya.

<sup>d</sup> Department of Chemistry, University of Cape Town, Rondebosch 7701, South Africa.

<sup>e</sup> Center of Scientific Excellence for Influenza Viruses, National Research Centre (NRC), Dokki, Giza 12622, Egypt.

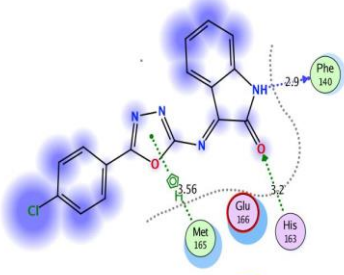
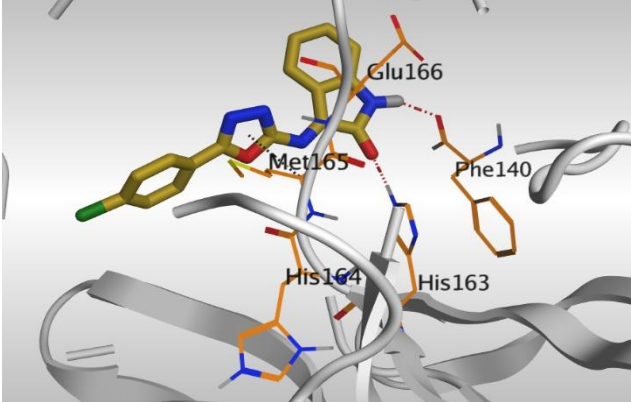
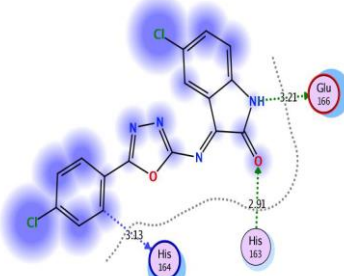
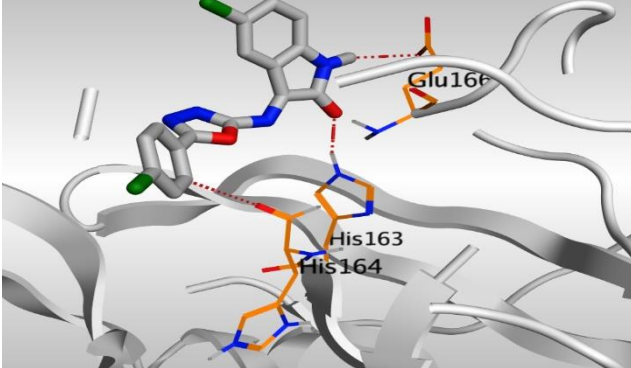
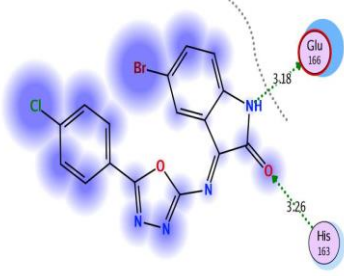
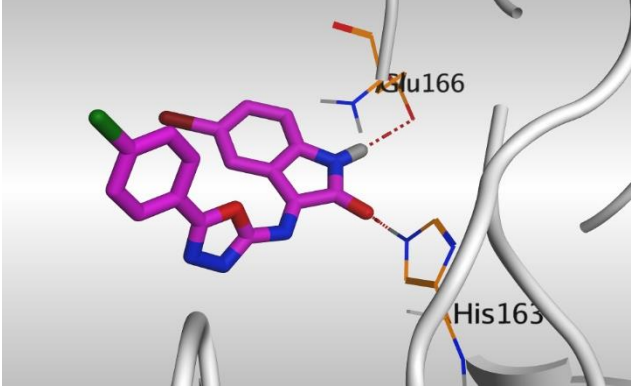
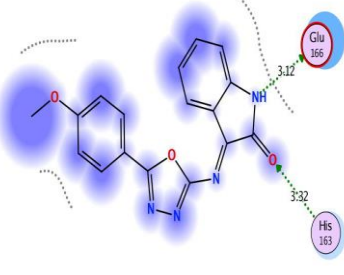
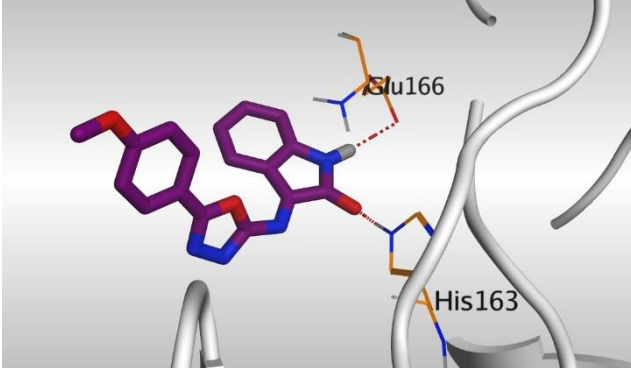
<sup>f</sup> Department of Pharmaceutical Organic Chemistry, Faculty of Pharmacy, Cairo University, Cairo, Egypt.

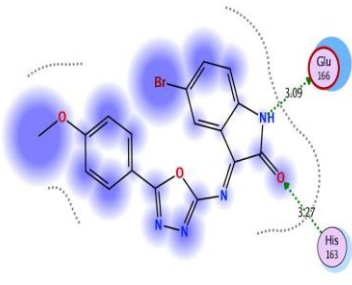
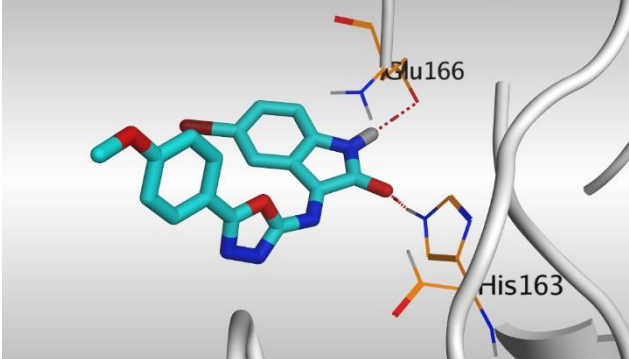
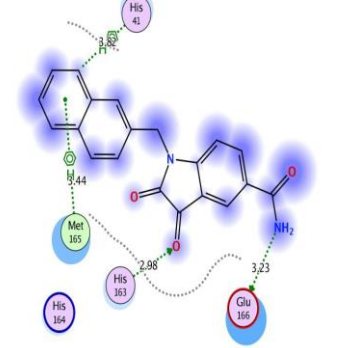
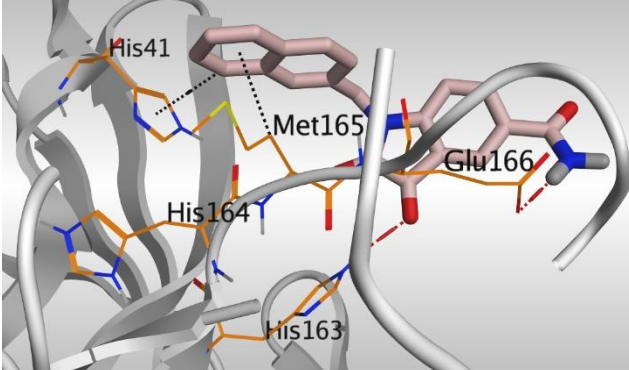
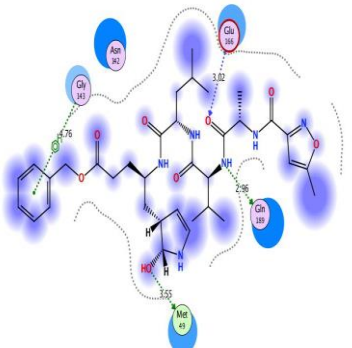
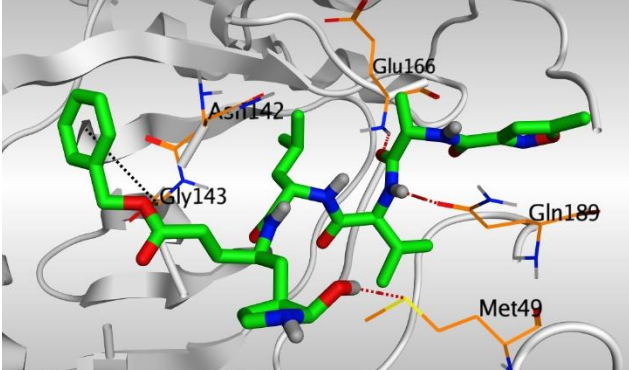
<sup>g</sup> Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Cairo University, Cairo, Egypt.

<sup>h</sup> Department of Organic Pharmaceutical Chemistry, Faculty of Pharmacy, October 6 University (O6U), October 6 city, Giza, Egypt.

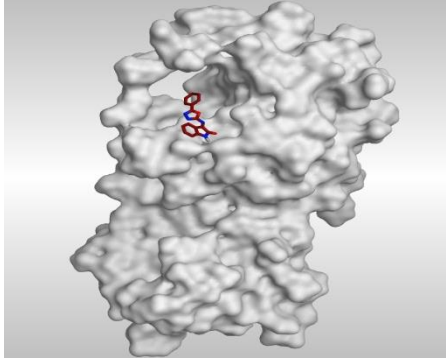
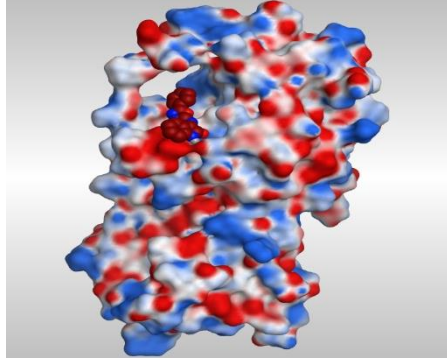
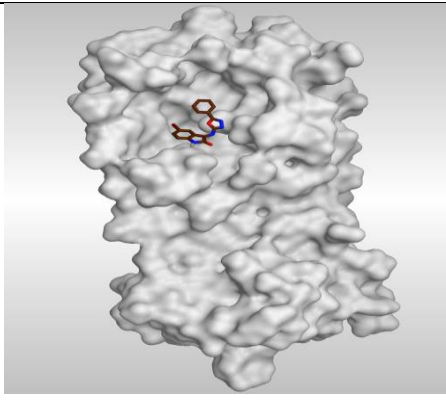
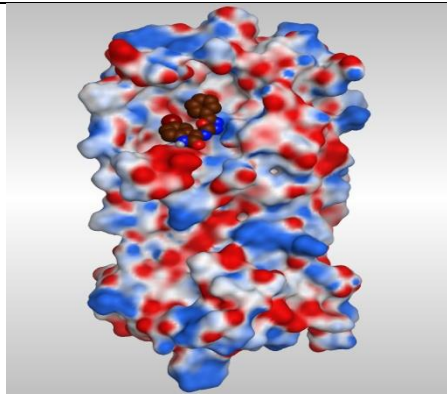
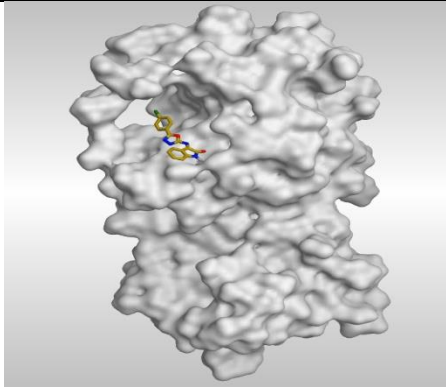
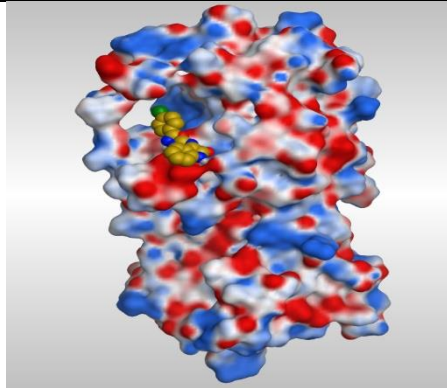
**Figure S11:** 2D and 3D docking representations of the seven newly synthesized Oxindole-Oxadiazole conjugates and the previously reported one (**Ia**) compared to the docked N3 inhibitor against its binding site inside the COVID-19 main protease.

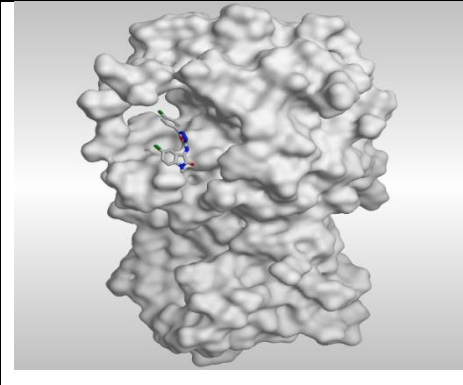
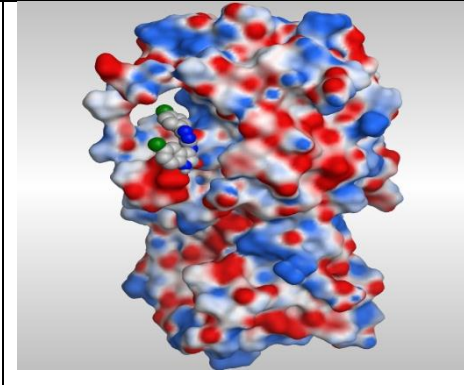
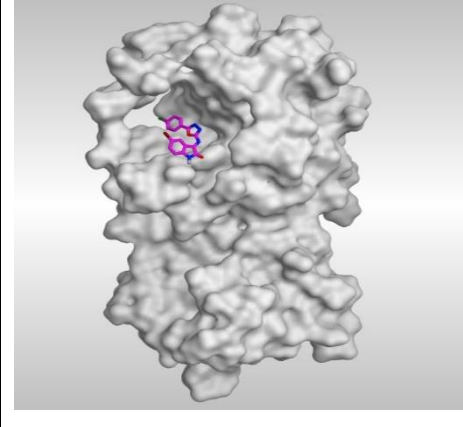
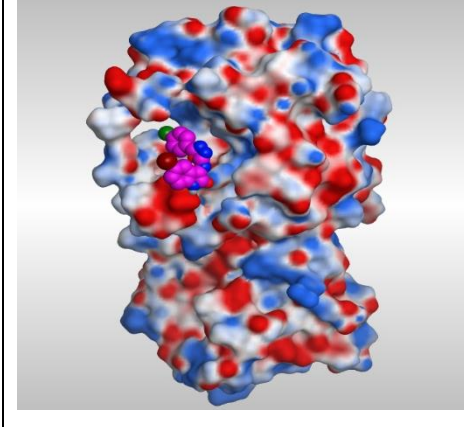
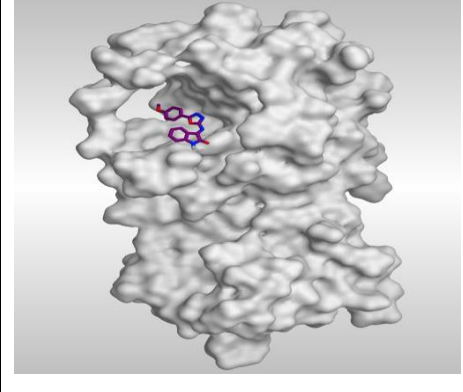
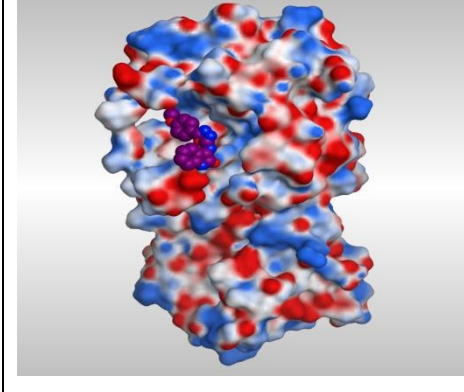
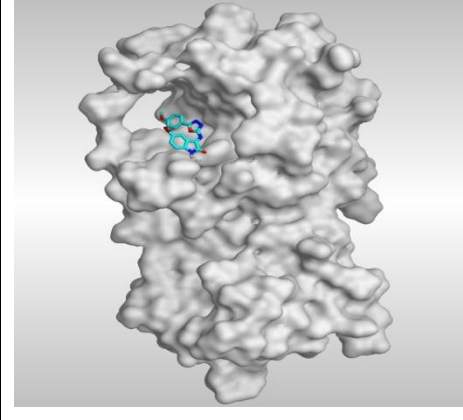
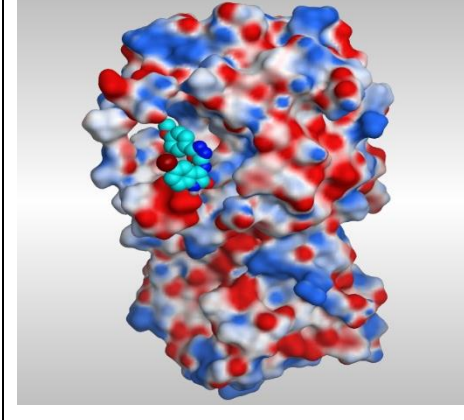
No.	Tested comp.	2D	3D
1	<b>III<sub>a</sub></b>		
2	<b>III<sub>b</sub></b>		

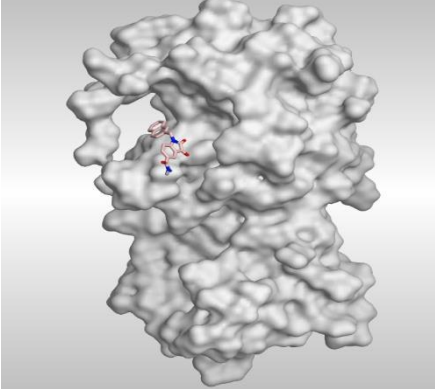
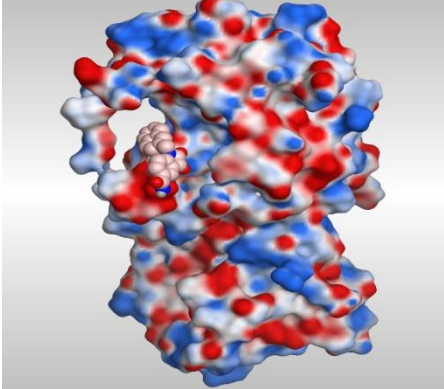
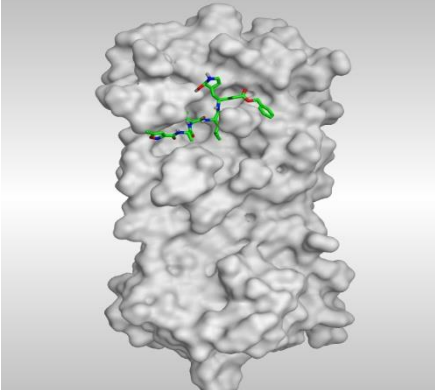
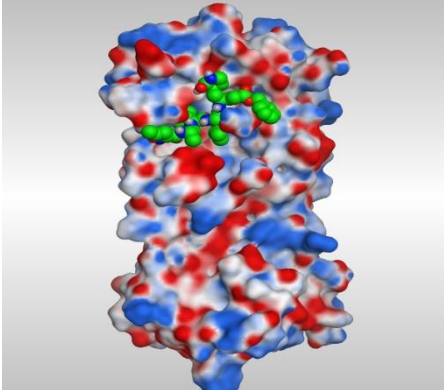
3	IIIc		
4	IIIa		
5	IIIe		
6	IIIf		

7	III <sub>g</sub>	 <p>2D chemical structure of III<sub>g</sub> showing hydrogen bonds (dotted lines) to Glu 166 (3.09 Å) and His 163 (3.27 Å). The molecule features a brominated benzimidazole core with a methoxy group and a phenyl ring.</p>	 <p>3D ribbon diagram of III<sub>g</sub> bound to a protein pocket. The ligand is shown in cyan and blue, interacting with Glu166 and His163 residues.</p>
8	I <sub>a</sub>	 <p>2D chemical structure of I<sub>a</sub> showing hydrogen bonds (dotted lines) to His 41 (3.44 Å), Met 165 (2.98 Å), His 164 (3.23 Å), and Glu 166 (3.23 Å). The molecule has a benzimidazole core with a phenyl ring and an amide group.</p>	 <p>3D ribbon diagram of I<sub>a</sub> bound to a protein pocket. The ligand is shown in pink and blue, interacting with His41, Met165, His164, His163, and Glu166 residues.</p>
9	N3	 <p>2D chemical structure of N3 showing hydrogen bonds (dotted lines) to Glu 166 (3.02 Å), Asn 142 (3.76 Å), Gly 143 (3.55 Å), Gln 189 (3.55 Å), and Met 49 (3.55 Å). The molecule is a complex polycyclic structure with multiple amide and ether groups.</p>	 <p>3D ribbon diagram of N3 bound to a protein pocket. The ligand is shown in green and blue, interacting with Glu166, Asn142, Gly143, Gln189, and Met49 residues.</p>

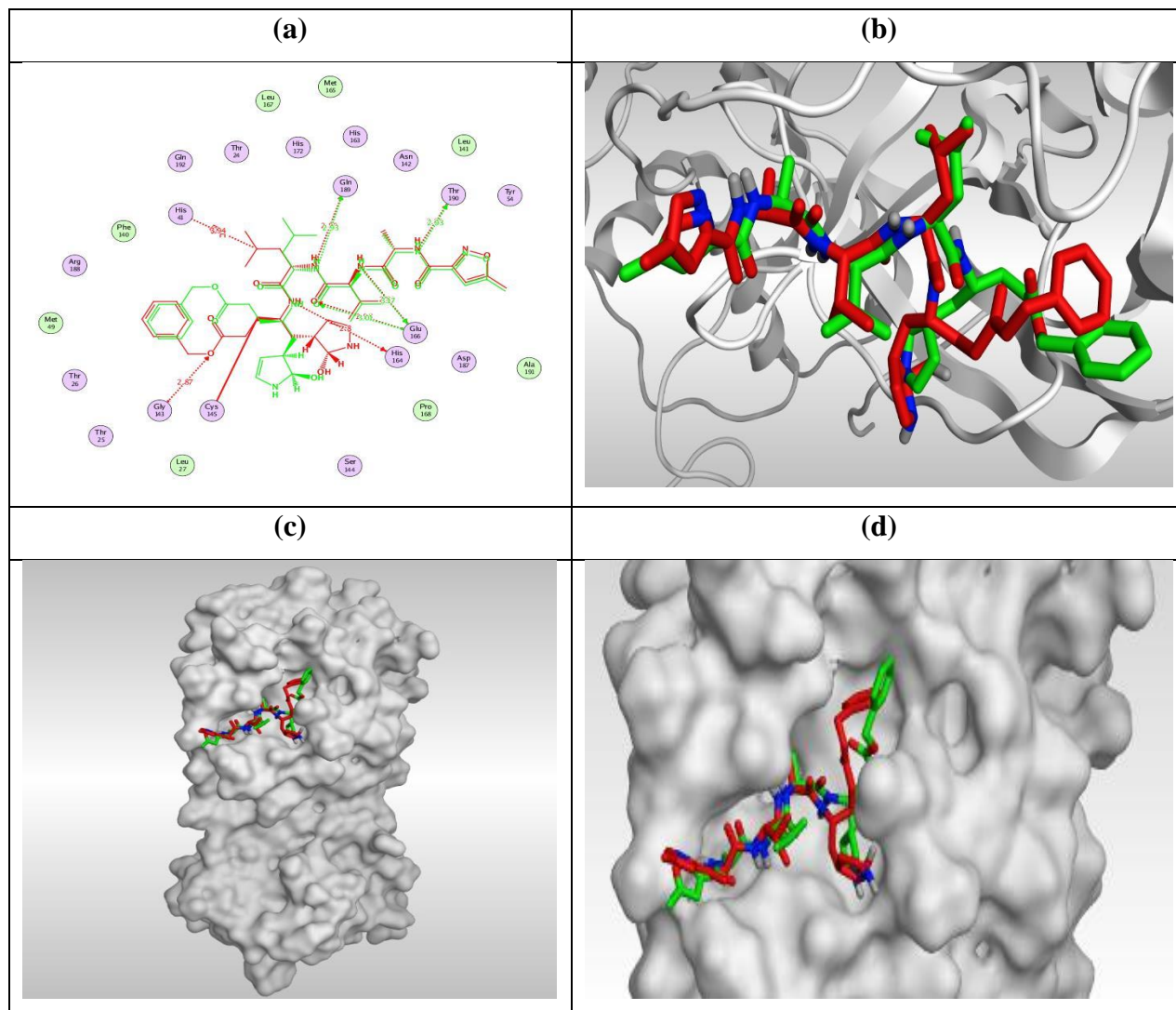
**Figure SI2:** A) Surface of the COVID-19 main protease pocket showing the positioning and fitting of the tested compounds, B) surface and maps of the tested compounds and the previously reported one (Ia) compared to the docked N3 inhibitor against its binding site inside the COVID-19 main protease.

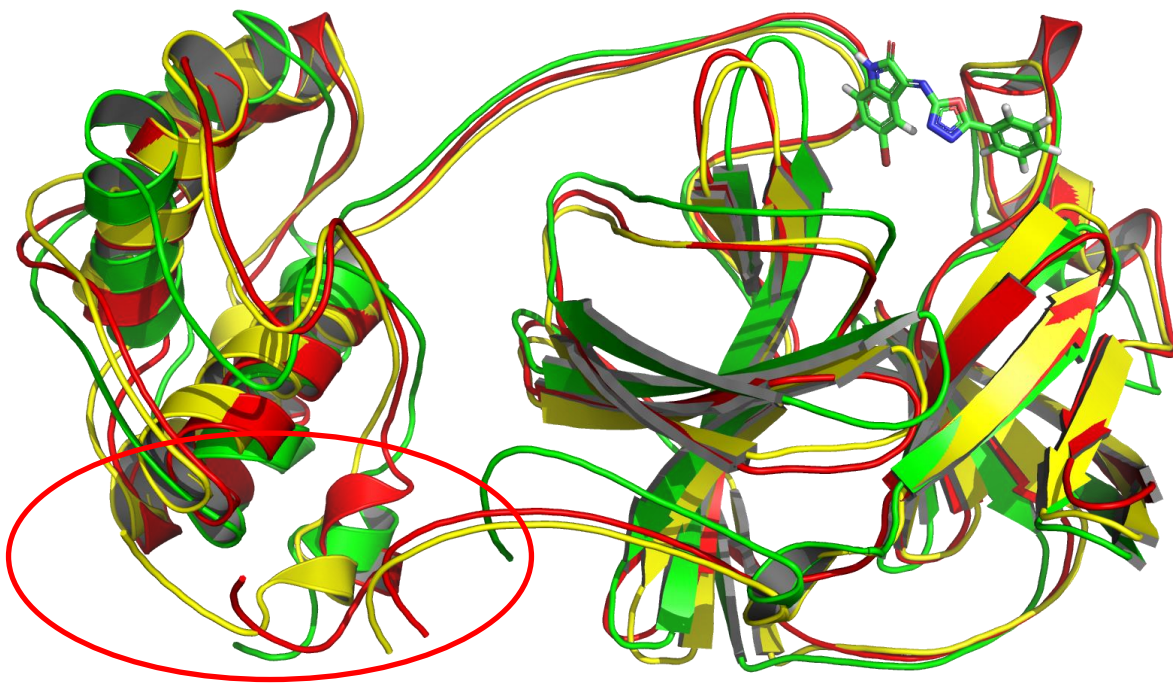
No.	Tested comp.	A	B
1	III <sub>a</sub>		
2	III <sub>b</sub>		
3	III <sub>c</sub>		

4	III <sub>d</sub>		
5	III <sub>e</sub>		
6	III <sub>f</sub>		
7	III <sub>g</sub>		

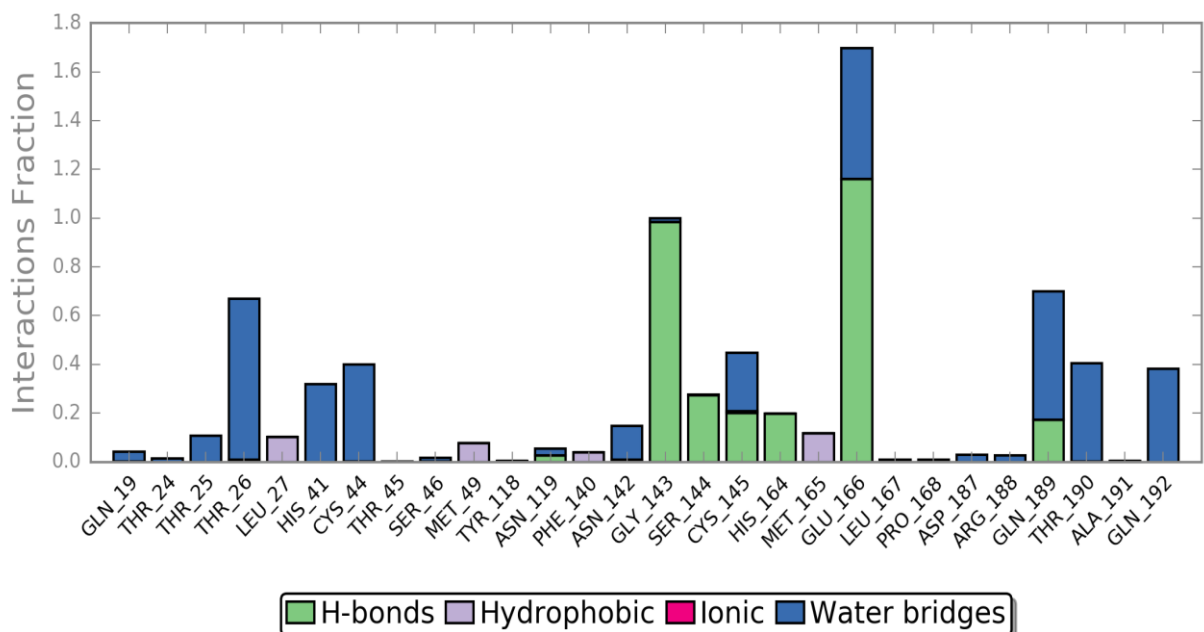
8	Ia	 A 3D surface model of a protein structure, labeled Ia. The protein is shown as a grey, textured surface. A small molecule, represented by a ball-and-stick model with red, blue, and white atoms, is bound within a pocket of the protein.	 An electrostatic potential surface representation of the protein Ia. The surface is colored in red (negative charge), blue (positive charge), and white (neutral). The small molecule from the previous image is shown in a ball-and-stick model within the protein's pocket.
9	N3	 A 3D surface model of a protein structure, labeled N3. The protein is shown as a grey, textured surface. A small molecule, represented by a ball-and-stick model with green, blue, and red atoms, is bound within a pocket of the protein.	 An electrostatic potential surface representation of the protein N3. The surface is colored in red (negative charge), blue (positive charge), and white (neutral). The small molecule from the previous image is shown in a ball-and-stick model within the protein's pocket.

**Figure SI3:** 2 D diagram (a), 3 D representation (b), and protein positioning (c and d) of the superimposition of the co-crystallized (red) and the docked pose (green), respectively, of N3 inhibitor inside the COVID-19 main protease binding site with RMSD of 1.46 Å.



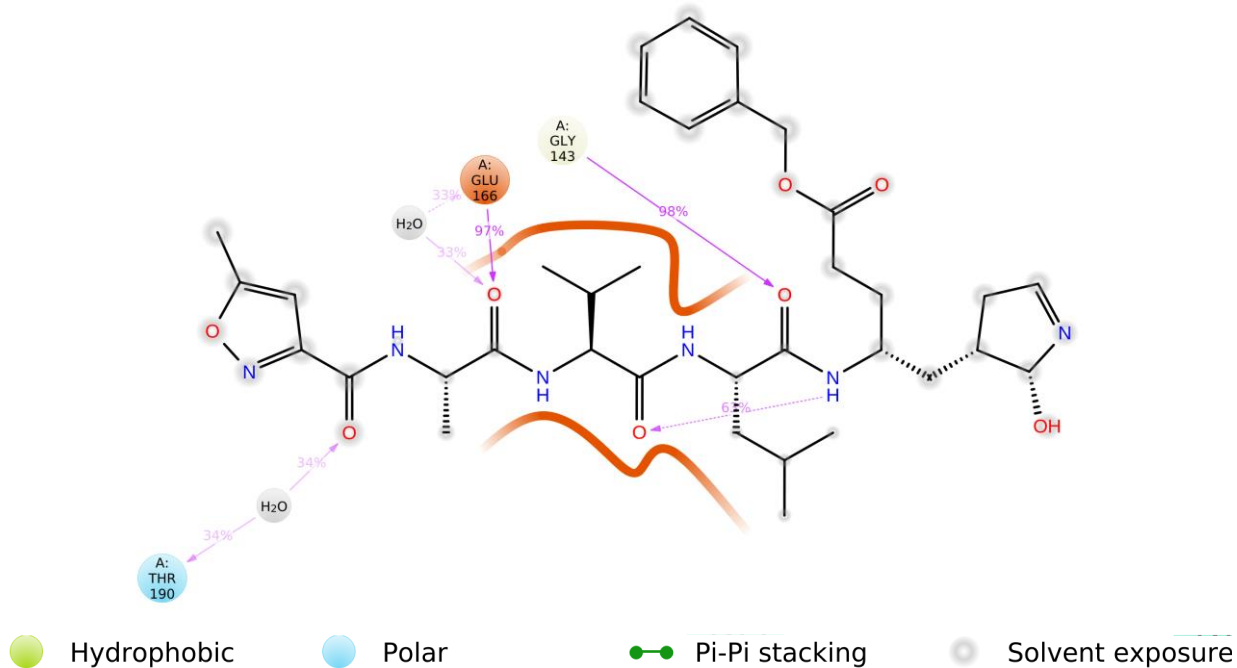


**Figure SI4:** The aligned structures of IVE\_4-6LU7 during simulation; green 0ns, yellow 50ns, red 100 ns.

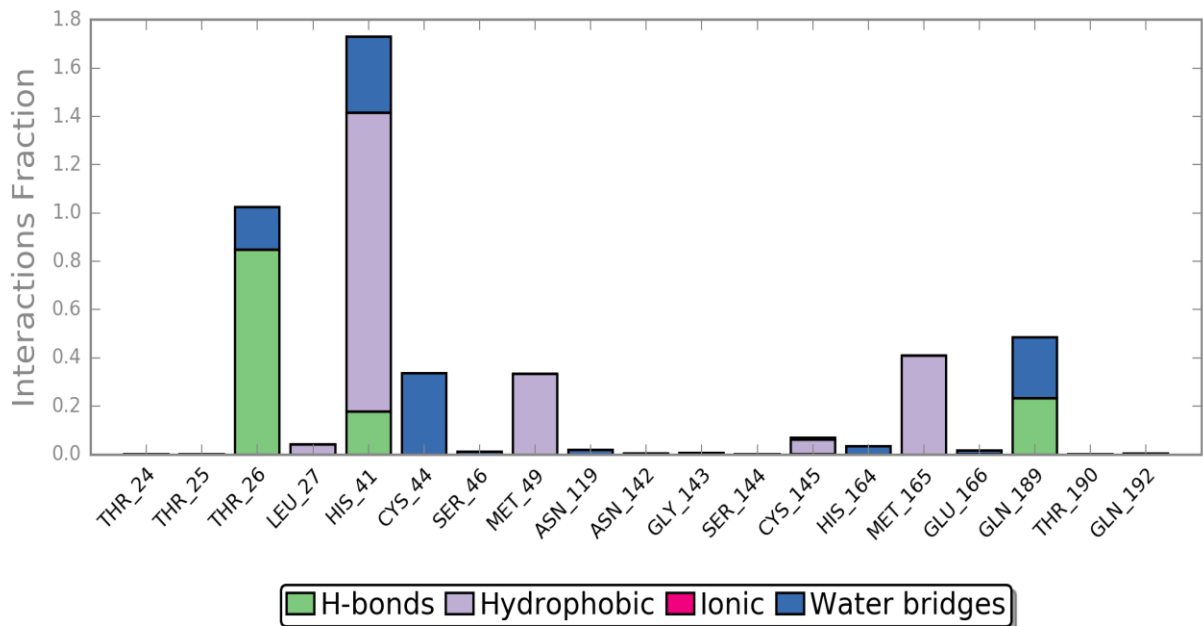


**Figure SI5:** The histogram of N3 – 6LU7 contact throughout the trajectory.

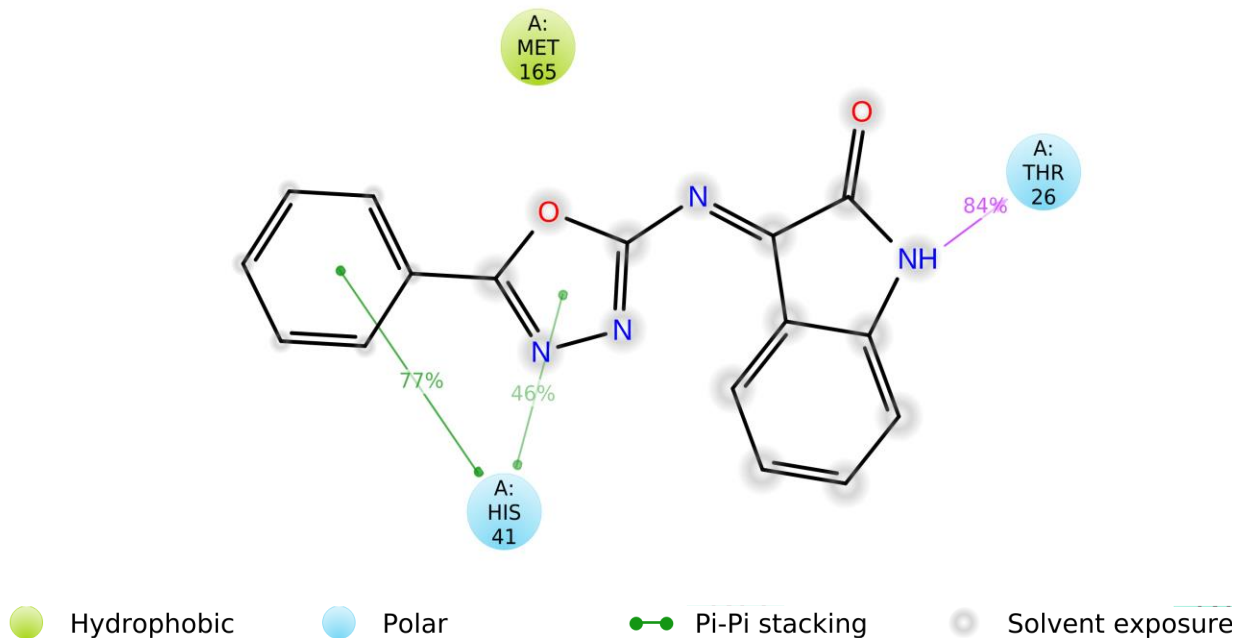




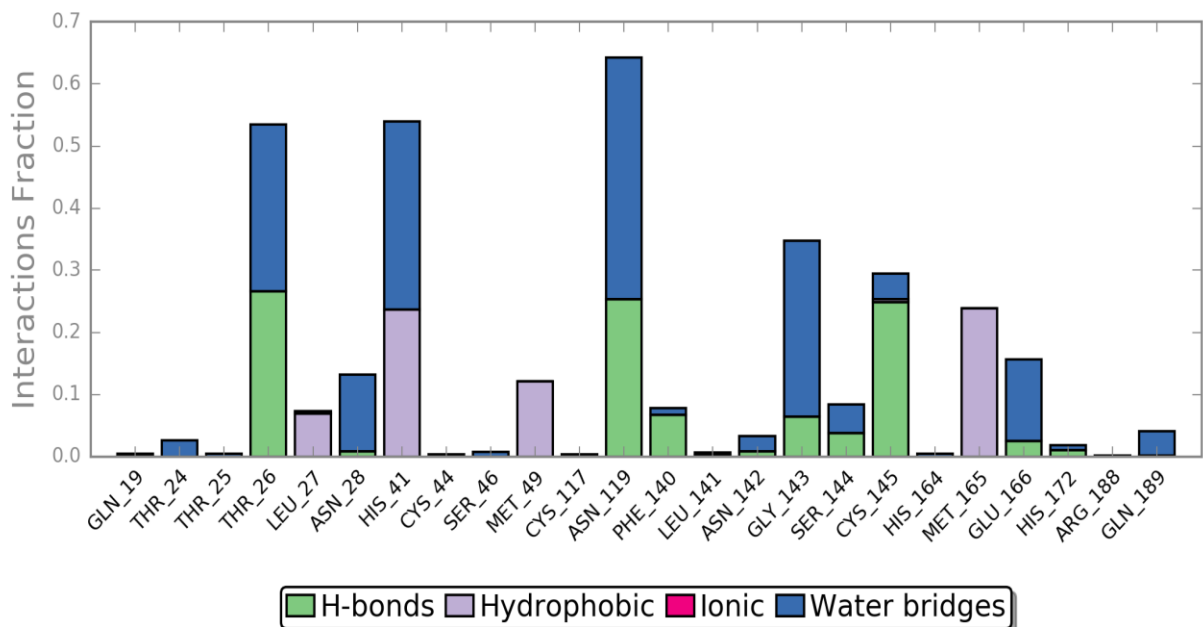
**Figure SI6:** The N3 – 6LU7 Interactions that occur more than 30.0% of the simulation time.



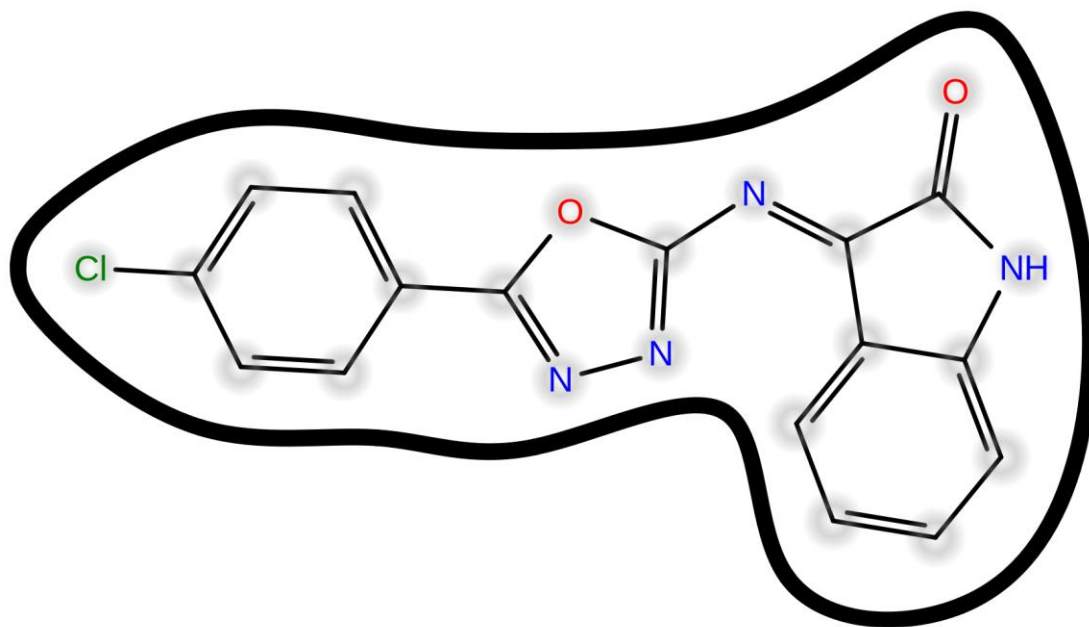
**Figure SI7:** The histogram of IVa – 6LU7 contact throughout the trajectory.



**Figure SI8:** The IVa – 6LU7 Interactions that occur more than 30.0% of the simulation time.

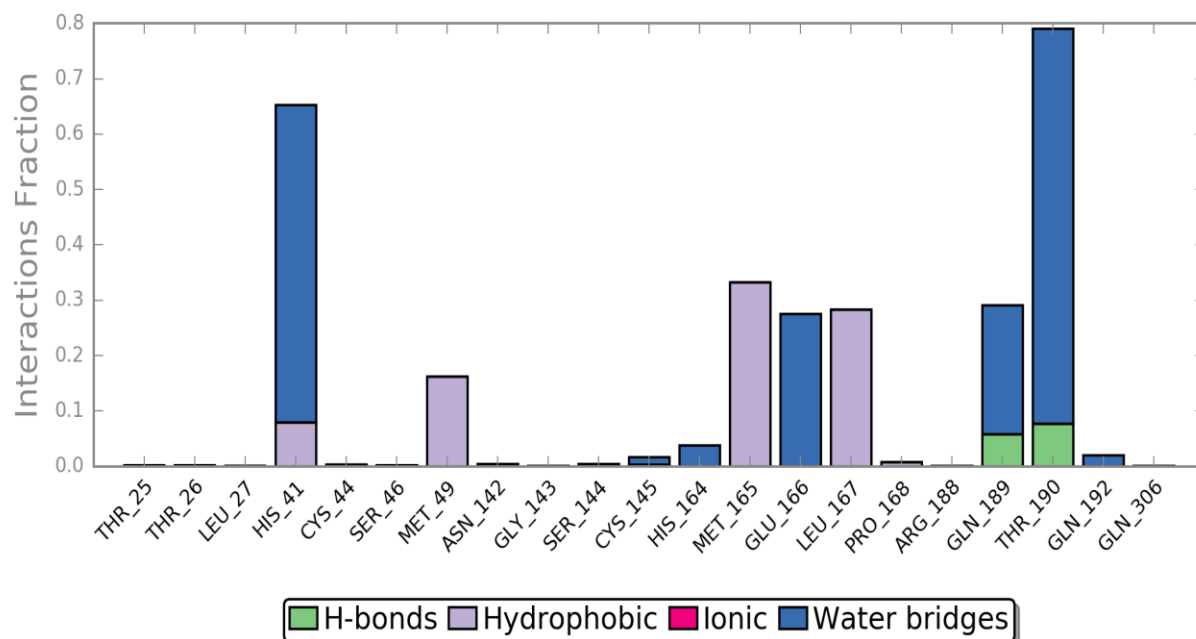


**Figure SI9:** The histogram of IVb – 6LU7 contact throughout the trajectory.

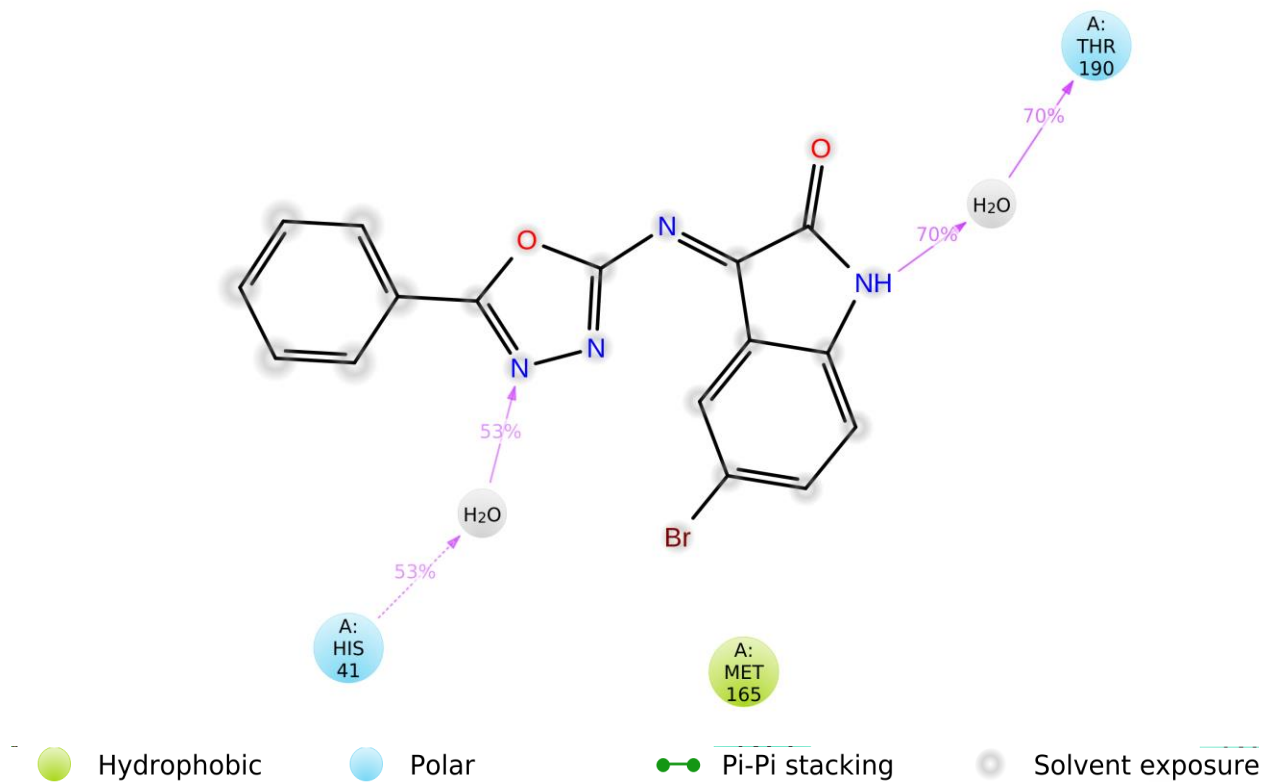


● Hydrophobic     
 ● Polar     
 —●— Pi-Pi stacking     
 ● Solvent exposure

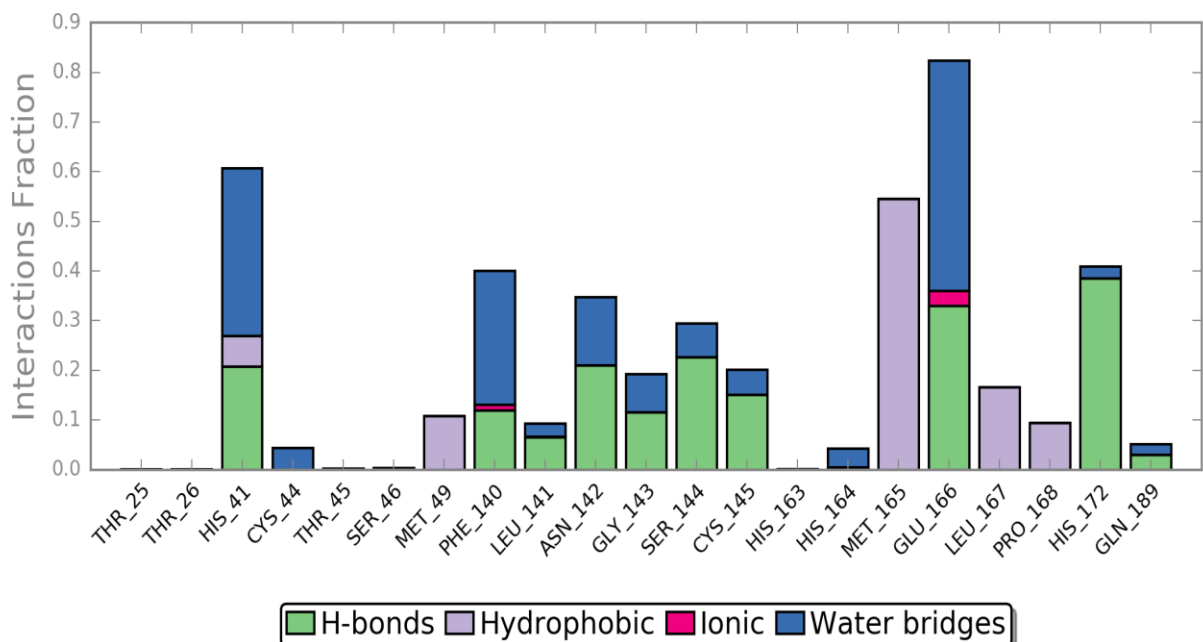
**Figure SI10:** The IV<sub>b</sub> – 6LU7 Interactions that occur more than 30.0% of the simulation time.



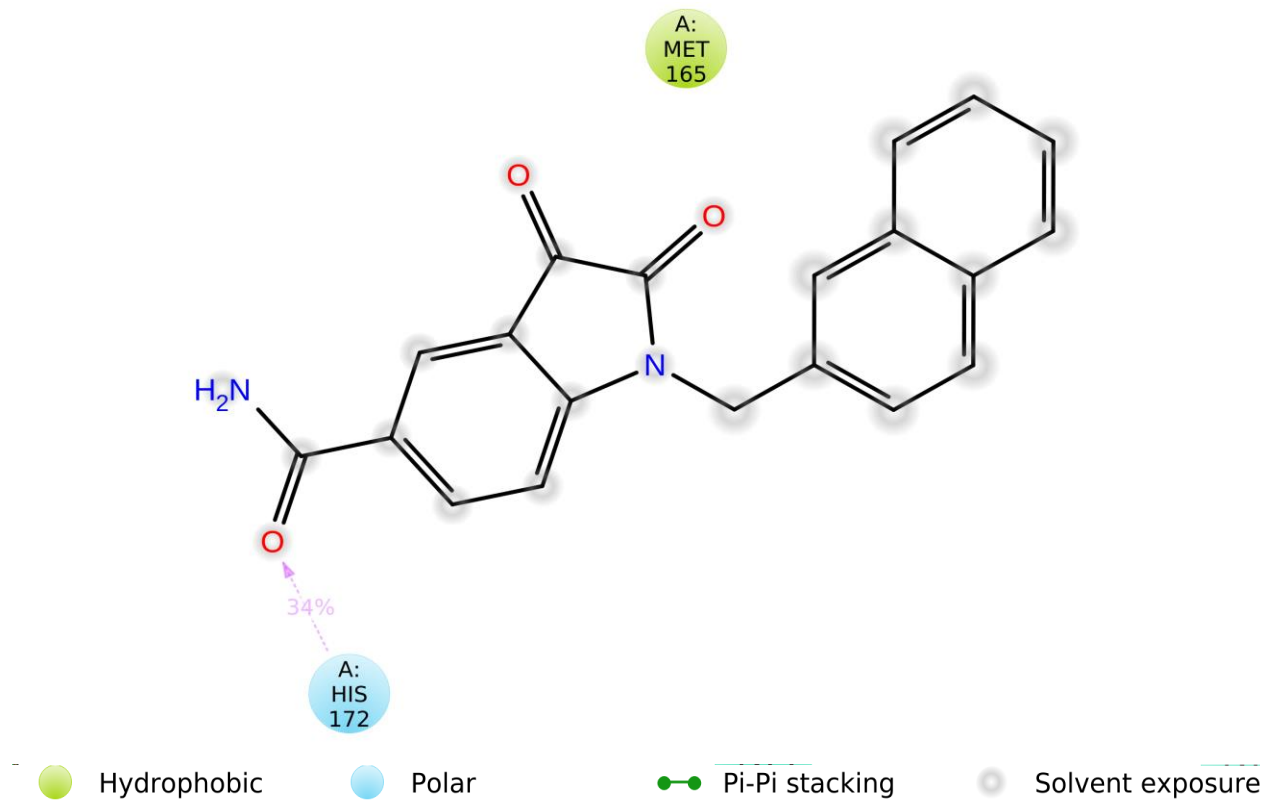
**Figure SI11:** The histogram of IV<sub>e</sub> – 6LU7 contact throughout the trajectory.



**Figure SI12:** The IV<sub>e</sub> – 6LU7 Interactions that occur more than 30.0% of the simulation time.



**Figure SI13:** The histogram of I<sub>a</sub> – 6LU7 contact throughout the trajectory.



**Figure SI14:** The I<sub>a</sub> – 6LU7 Interactions that occur more than 30.0% of the simulation time.