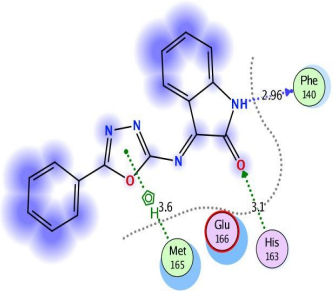
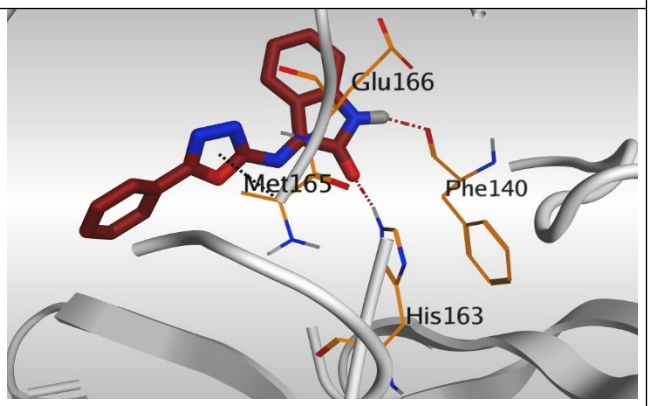
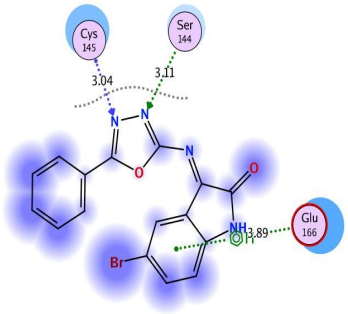
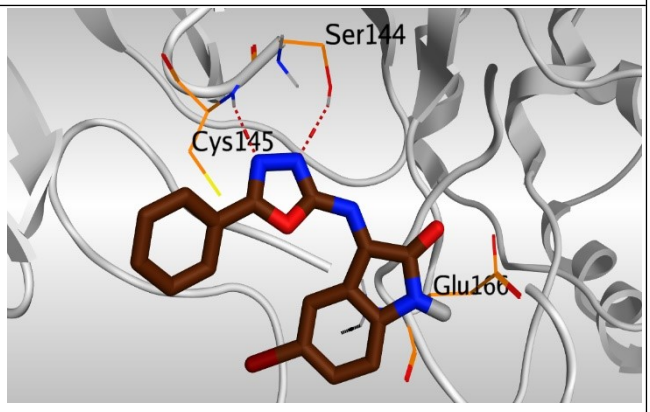
Electronic Supplementary Material (ESI) for New Journal of Chemistry.

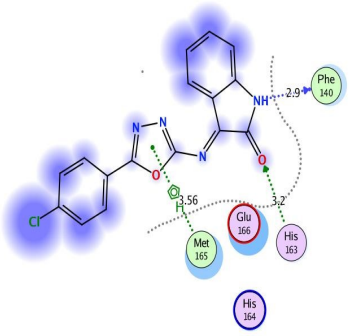
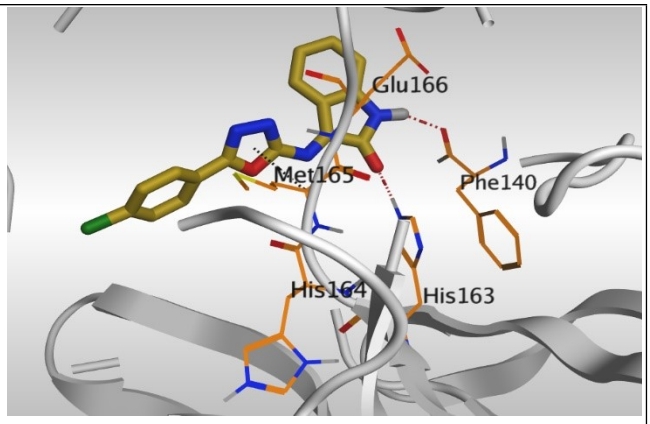
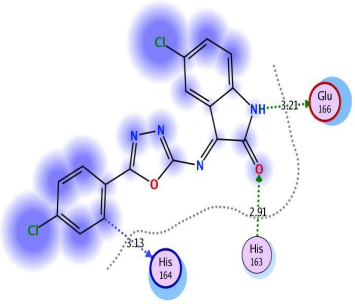
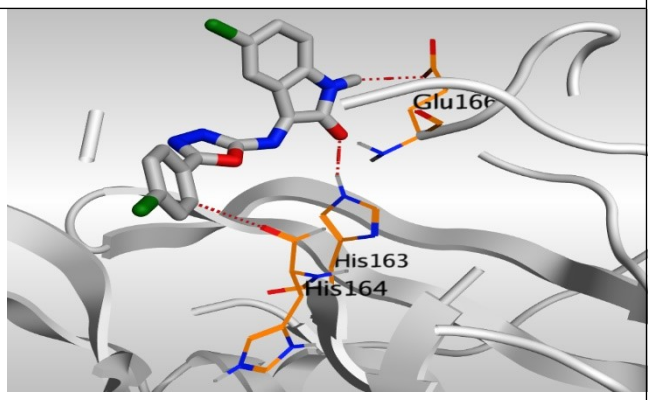
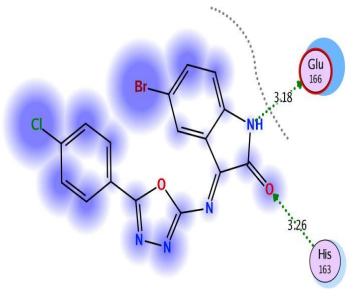
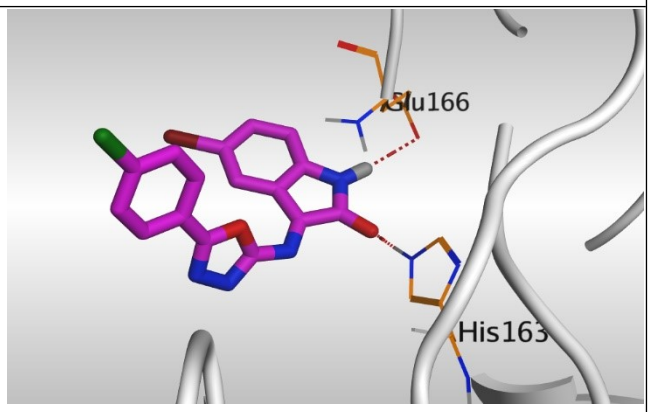
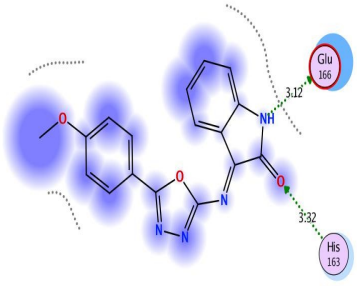
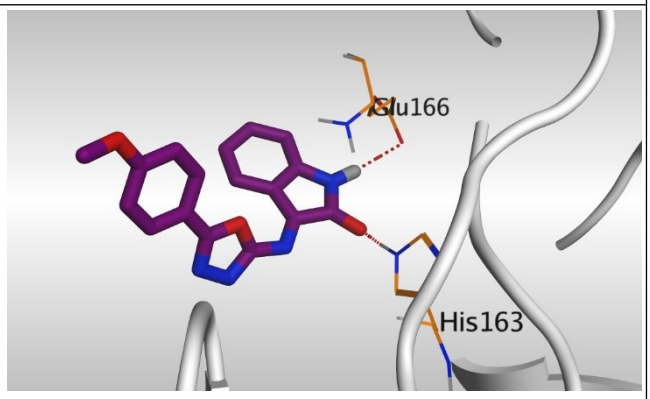
Newly Synthesized Series of Oxoindole-Oxadiazole Conjugates as Potential Anti-SARS-CoV-2 Agents: *In Silico* and *In Vitro* Studies

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

[a] Organic Chemistry Department, Faculty of Pharmacy, October University for Modern Sciences and Arts (MSA), October 6 city, Giza, Egypt
[b] Department of Pharmaceutical Medicinal Chemistry, Faculty of Pharmacy, Horus University-Egypt, New Damietta 34518, Egypt.
[c] Department of Chemistry, Faculty of Science, University of Benghazi, Benghazi, Libya.
[d] Department of Chemistry, University of Cape Town, Rondebosch 7701, South Africa.
[e] Center of Scientific Excellence for Influenza Viruses, National Research Centre (NRC), Dokki, Giza 12622, Egypt.
[f] Department of Pharmaceutical Organic Chemistry, Faculty of Pharmacy, Cairo University, Cairo, Egypt.
[g] Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Cairo University, Cairo, Egypt.
[h] Department of Organic Pharmaceutical Chemistry, Faculty of Pharmacy, October 6 University (O6U), October 6 city, Giza, Egypt.

Figure SI1: 2D and 3D docking representations of the seven newly synthesized Oxoindole-Oxadiazole conjugates and the previously reported one ($\mathbf{I_a}$) compared to the docked **N3** inhibitor against its binding site inside the COVID-19 main protease.

No.	Tested comp.	2D	3D
		polar, acidic, basic, greasy, proximity contour; sidechain acceptor, sidechain donor, backbone acceptor, backbone donor; solvent residue, metal complex, solvent contact, metal/ion contact; ligand exposure, receptor exposure; arene-arene, arene-H, arene-cation	Red dashed lines refer to hydrogen bonds, while the black ones denote hydrophobic interactions.
1	$\mathbf{III_a}$		
2	$\mathbf{III_b}$		

3	**III_c**		
4	**III_d**		
5	**III_e**		
6	**III_f**		

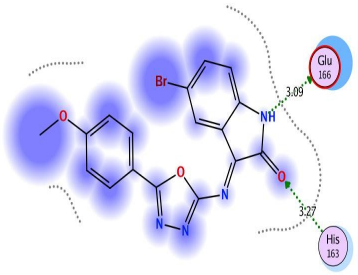
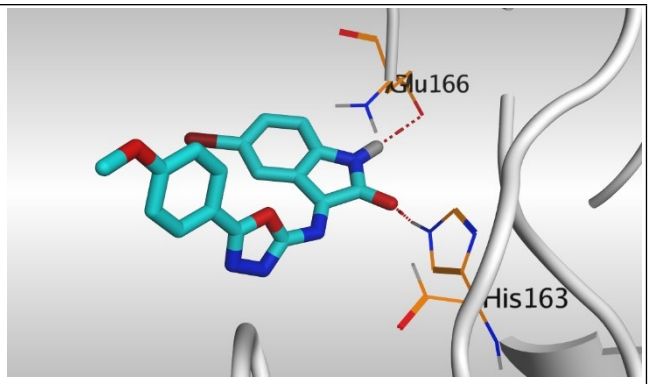
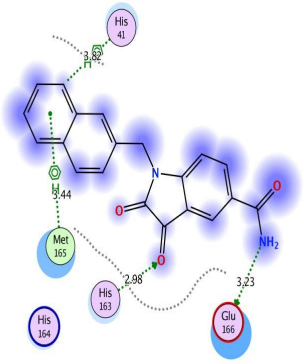
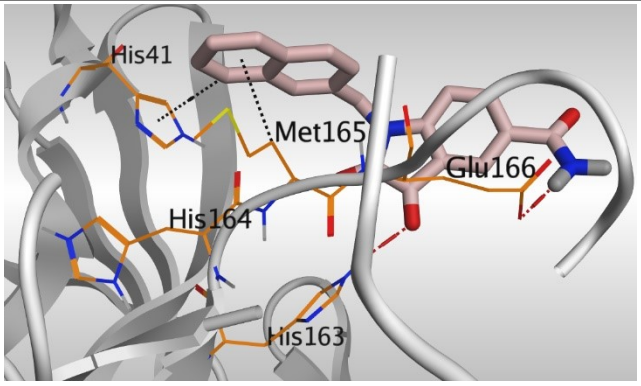
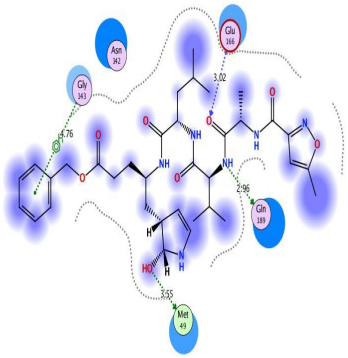
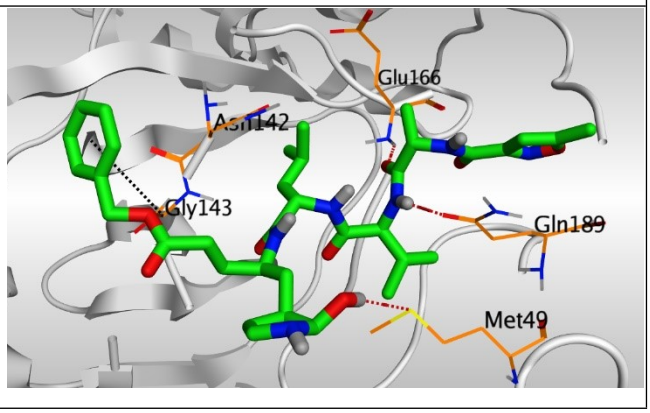
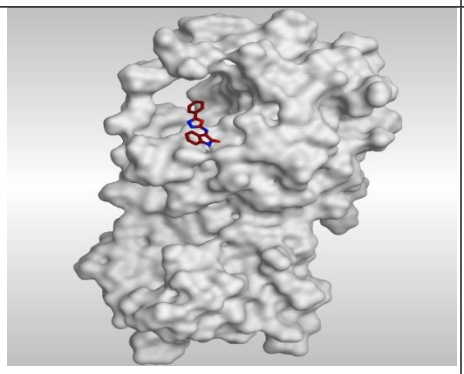
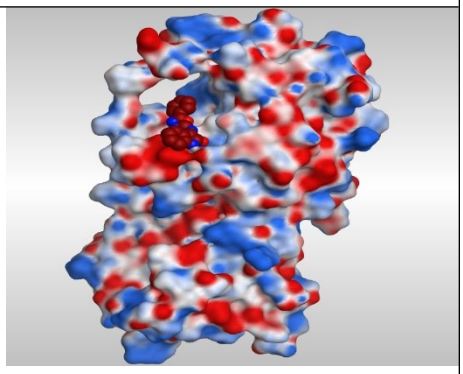
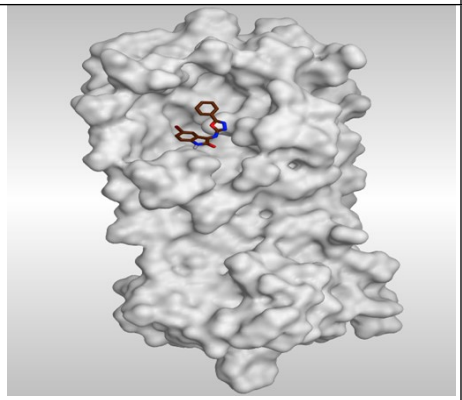
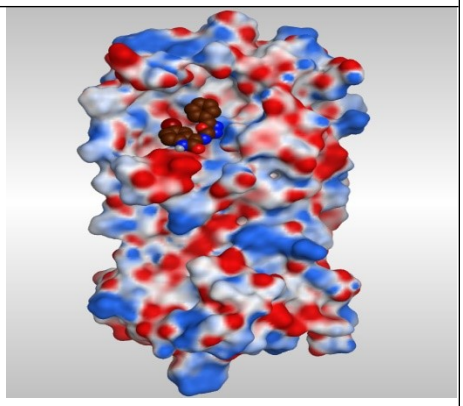
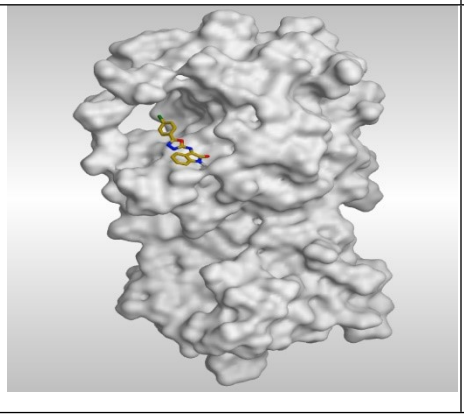
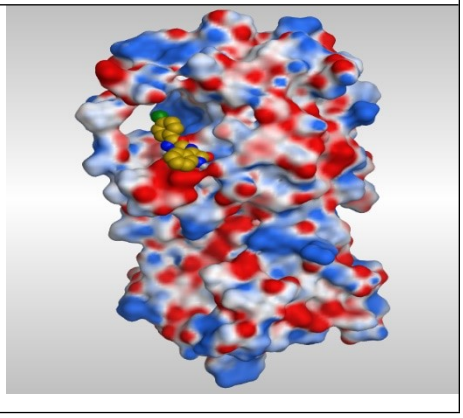
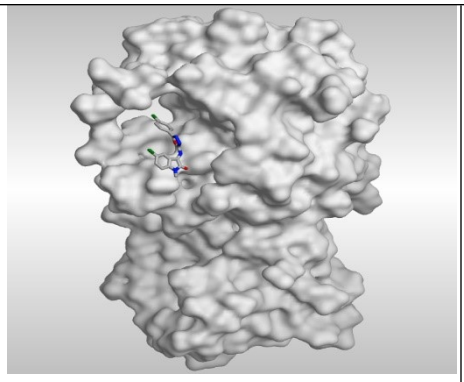
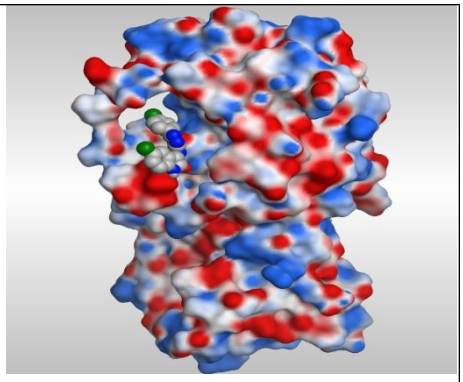
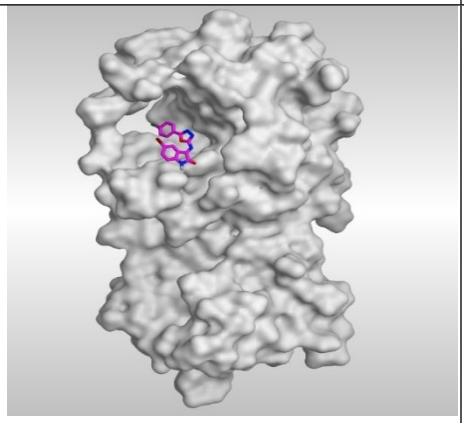
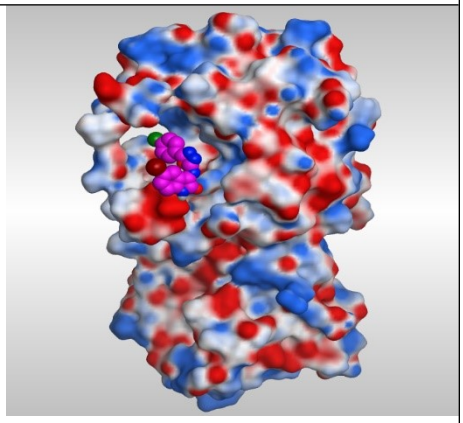
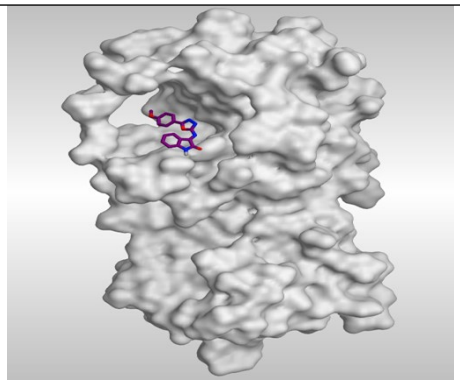
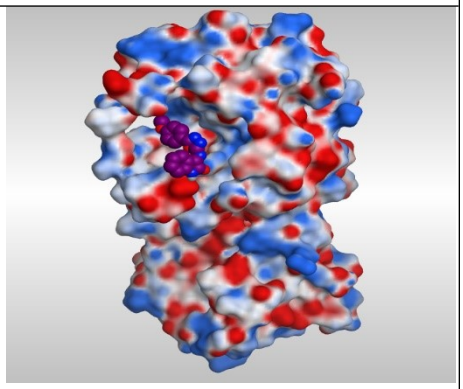
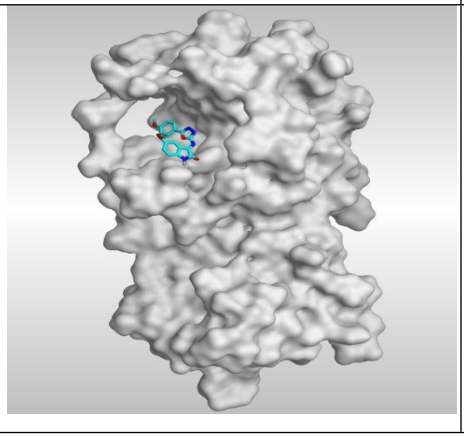
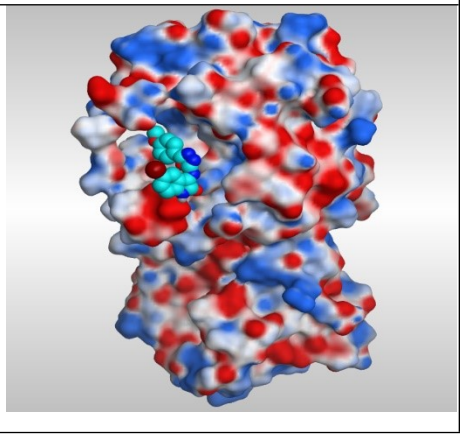
7	**III_g**		
8	**I_a**		
9	**N3**		

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_a		
2	III_b		
3	III_c		

4	**III_d**		
5	**III_e**		
6	**III_f**		
7	**III_g**		

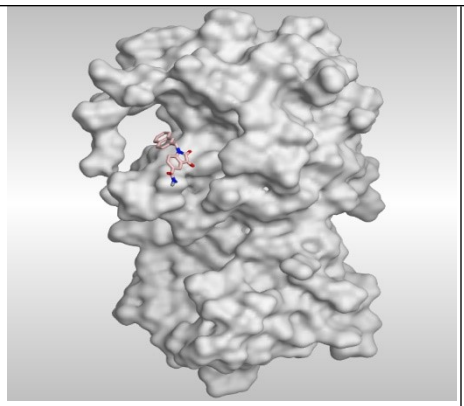
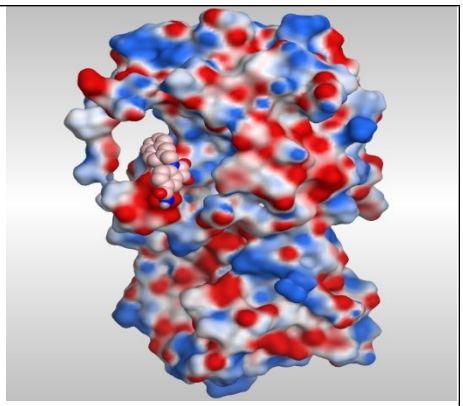
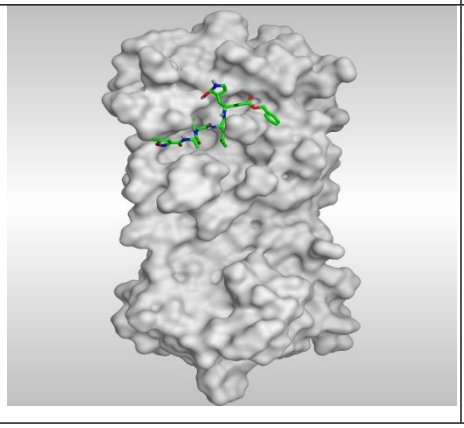
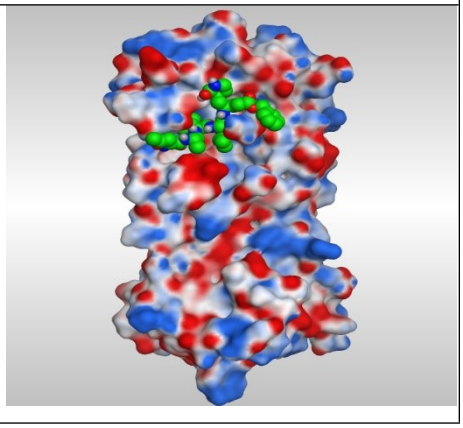
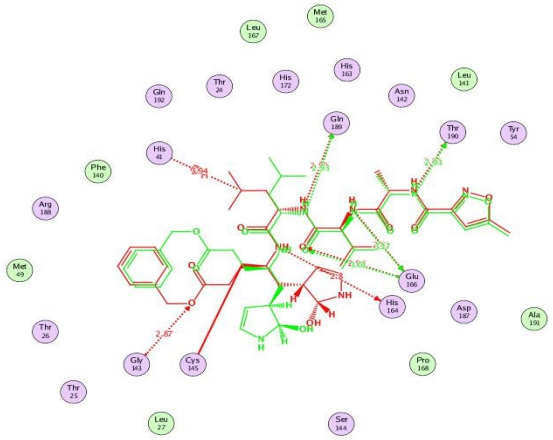
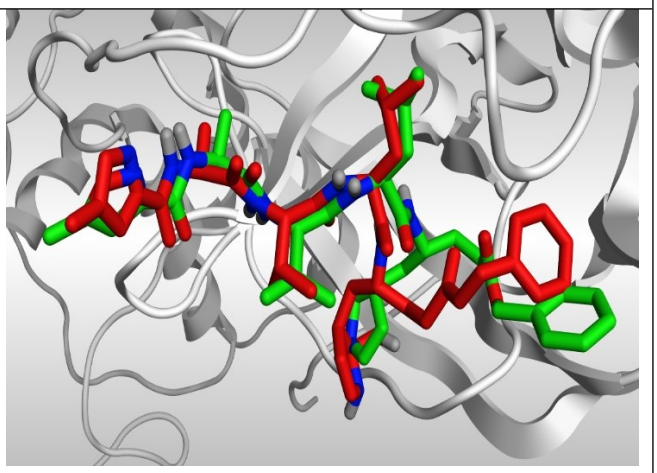
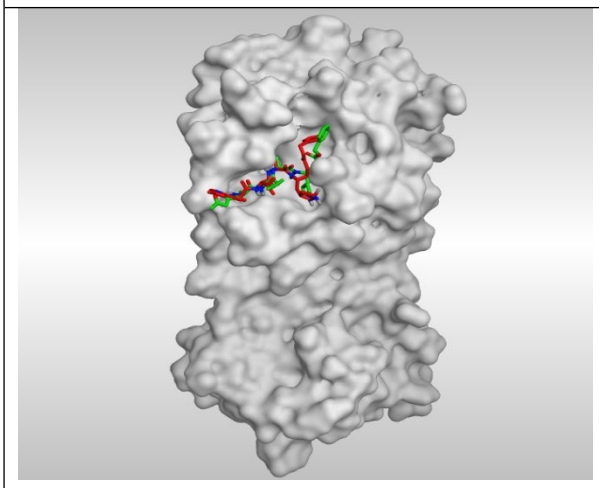
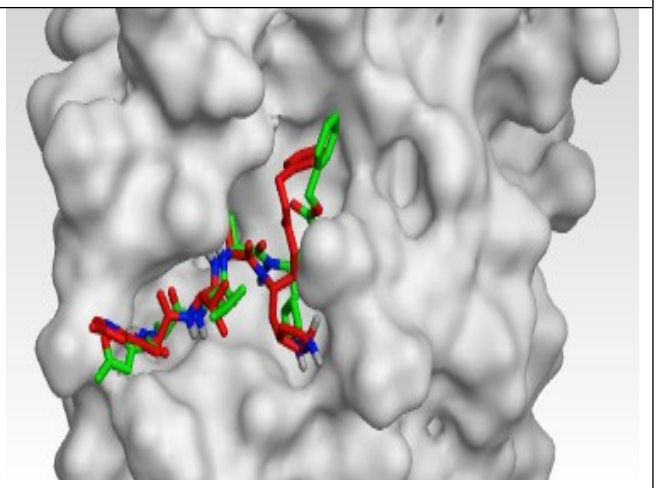
8	**I_a**		
9	**N3**		

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.

(a)	(b)
	
(c)	**(d)**
	

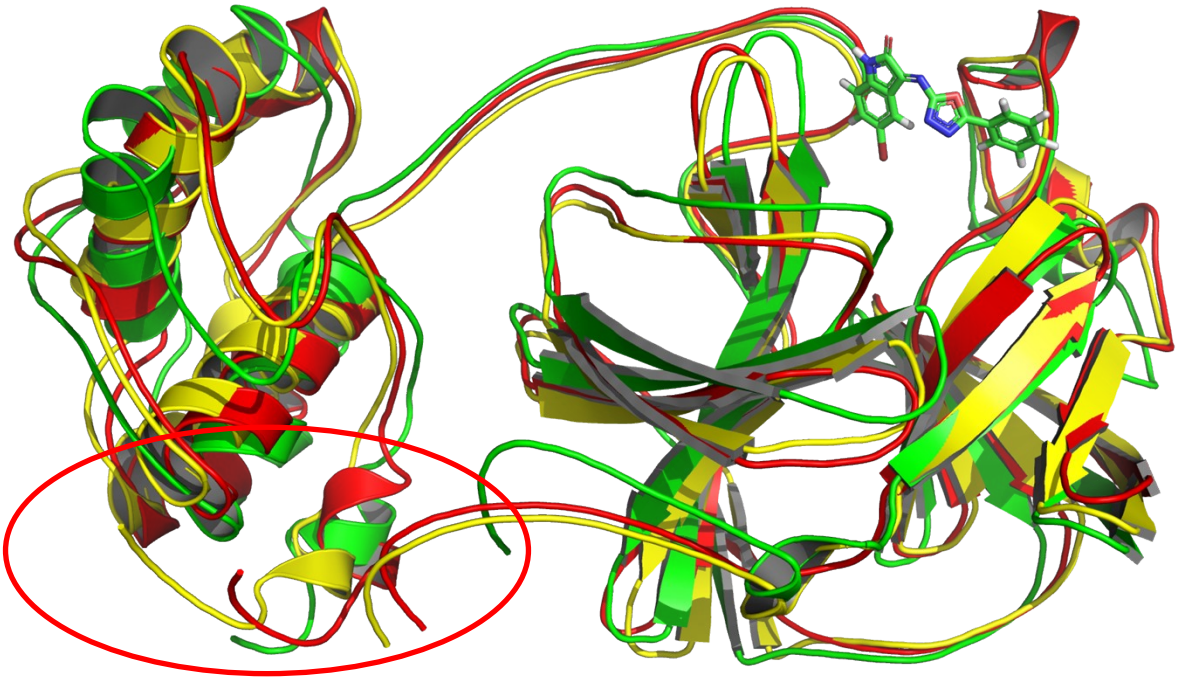


Figure SI4: The aligned structures of IVe_4-6LU7 during simulation; green 0ns, yellow 50ns, red 100 ns.

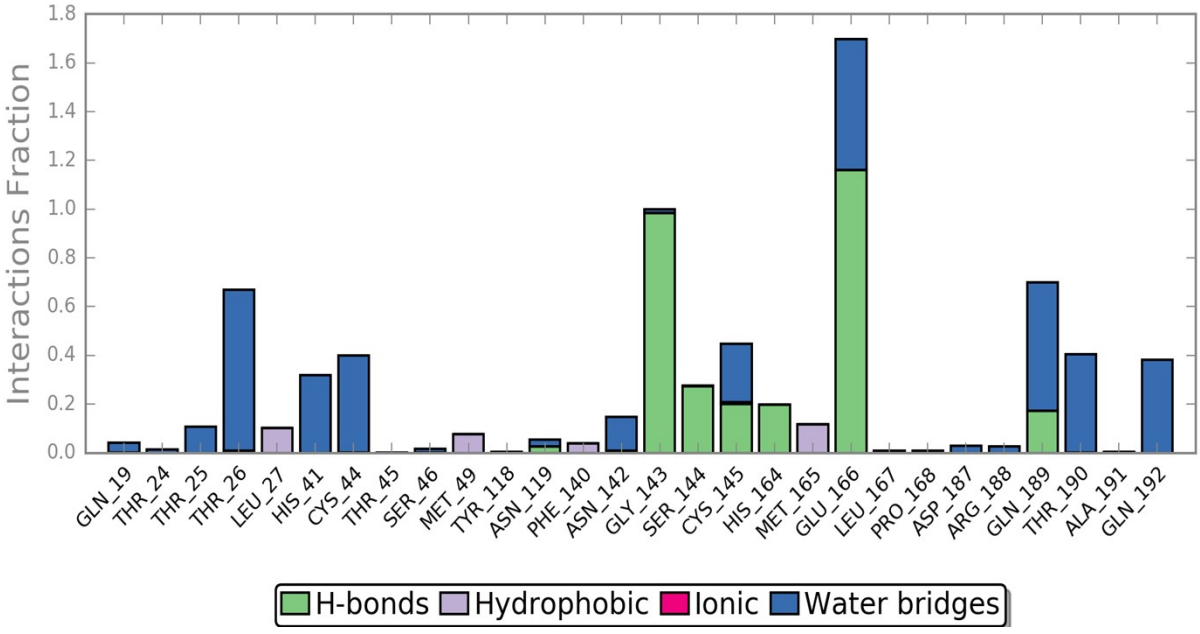


Figure SI5: The histogram of N3 – 6LU7 contact throughout the trajectory.

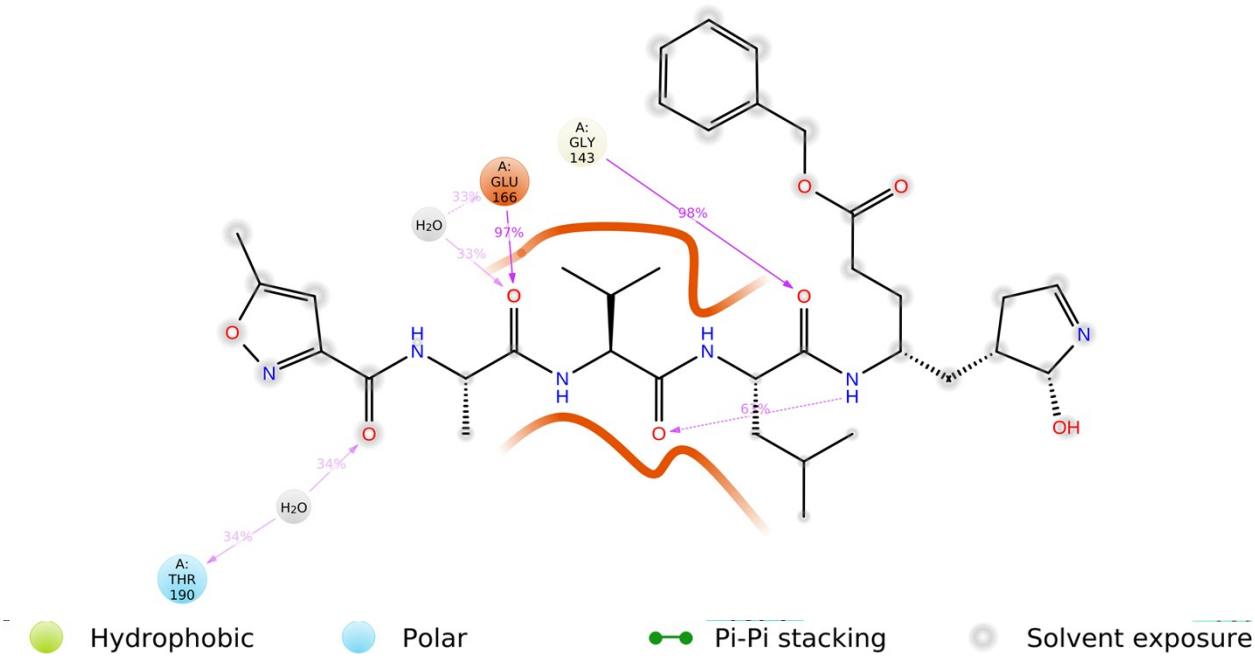


Figure SI6: The N3 – 6LU7 Interactions that occur more than 30.0% of the simulation time.

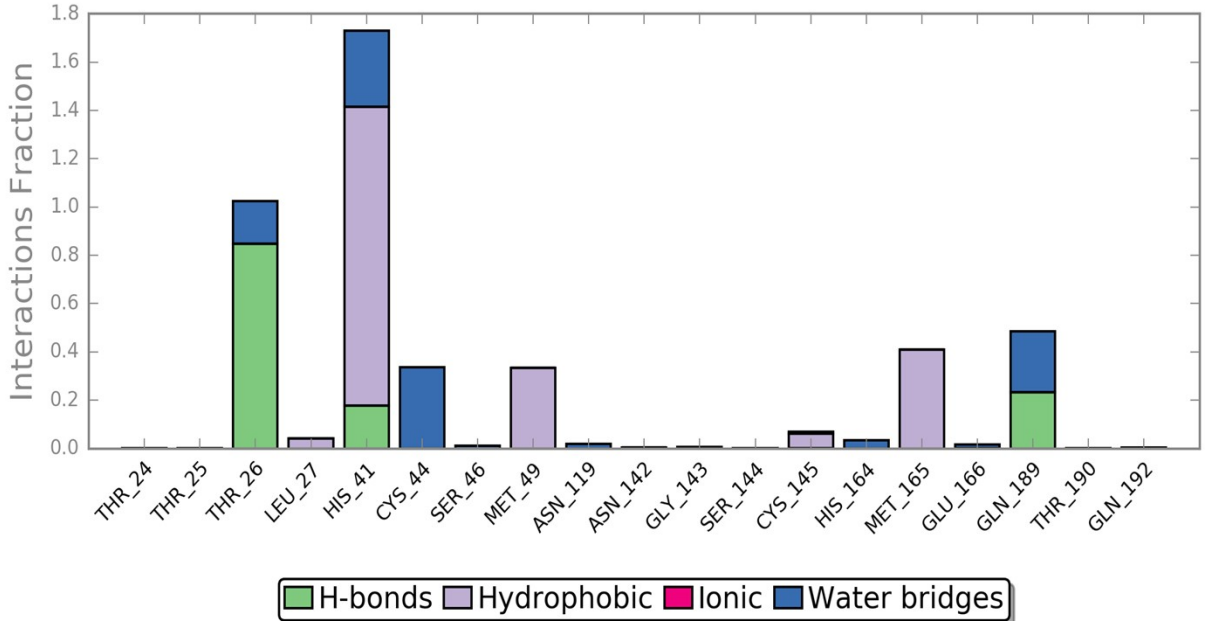


Figure SI7: The histogram of IVa – 6LU7 contact throughout the trajectory.

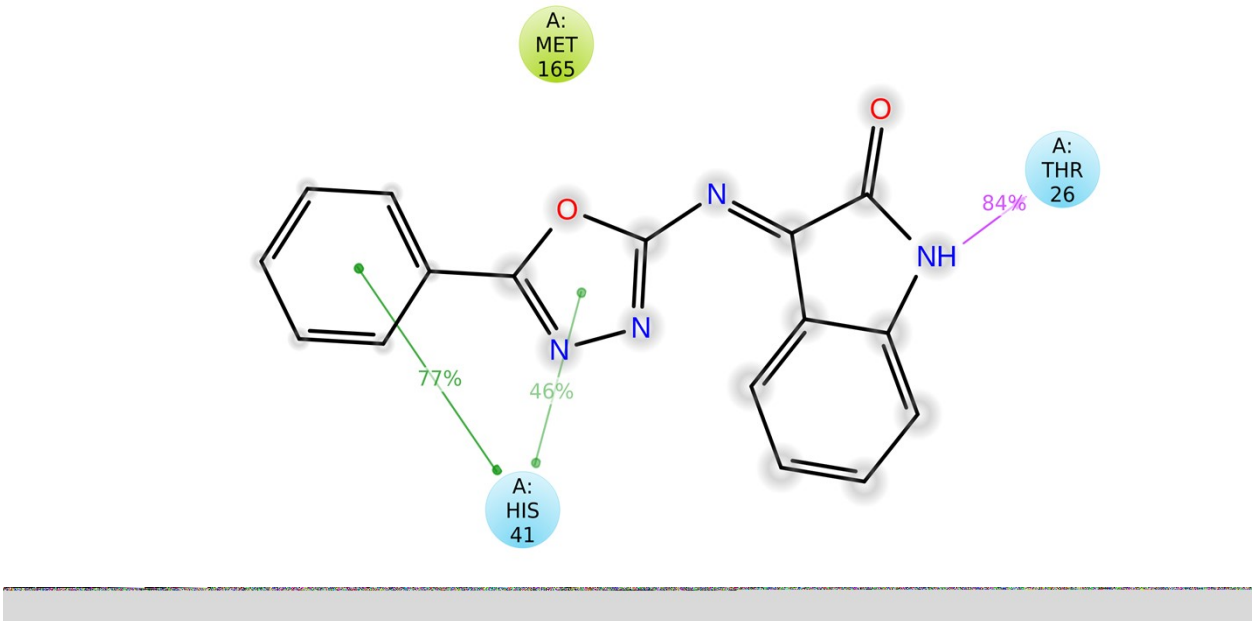


Figure SI8: The IVa – 6LU7 Interactions that occur more than 30.0% of the simulation time.

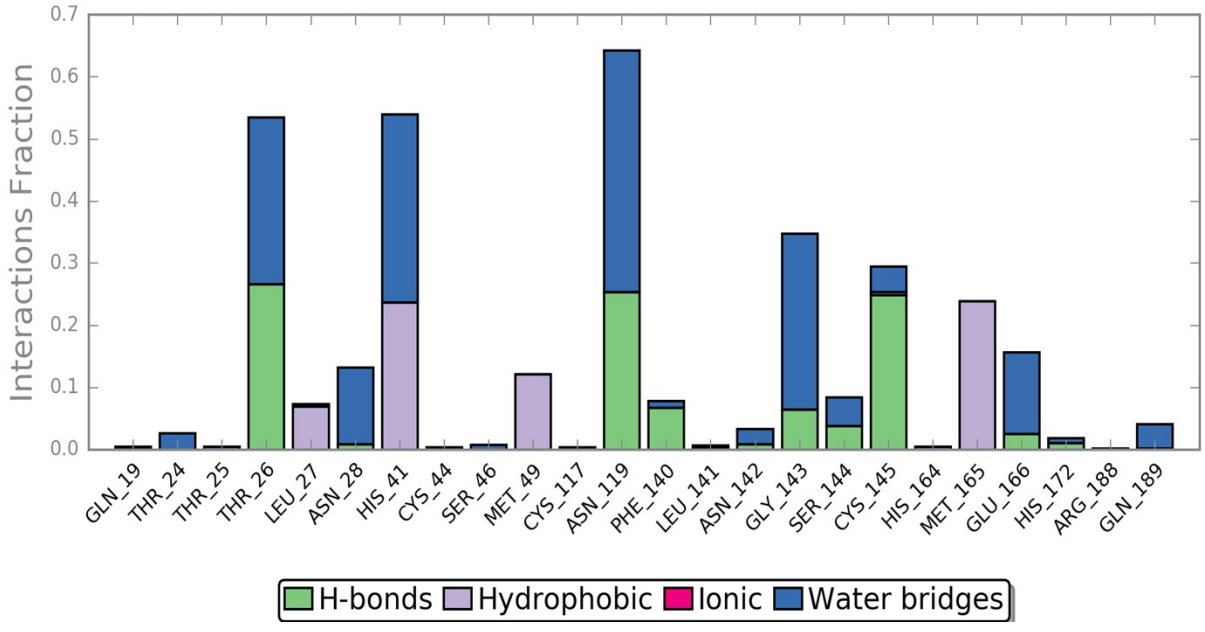


Figure SI9: The histogram of IVb – 6LU7 contact throughout the trajectory.

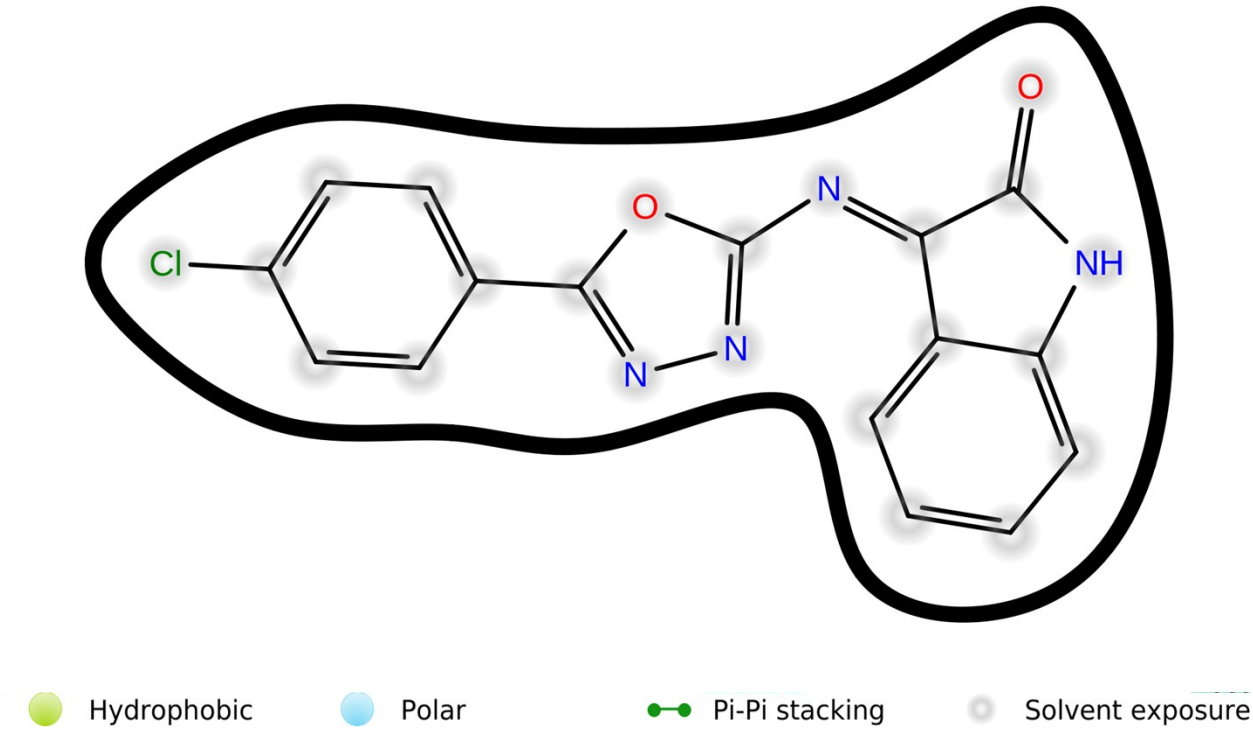


Figure SI10: The IV_b – 6LU7 Interactions that occur more than 30.0% of the simulation time.

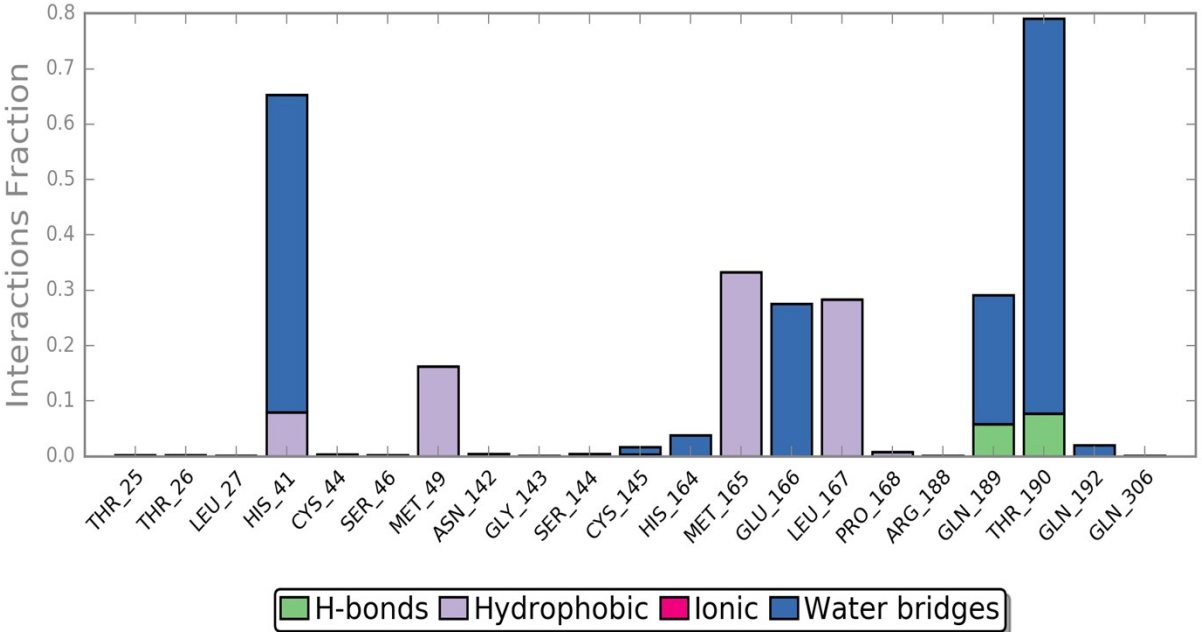


Figure SI11: The histogram of IV_e – 6LU7 contact throughout the trajectory.

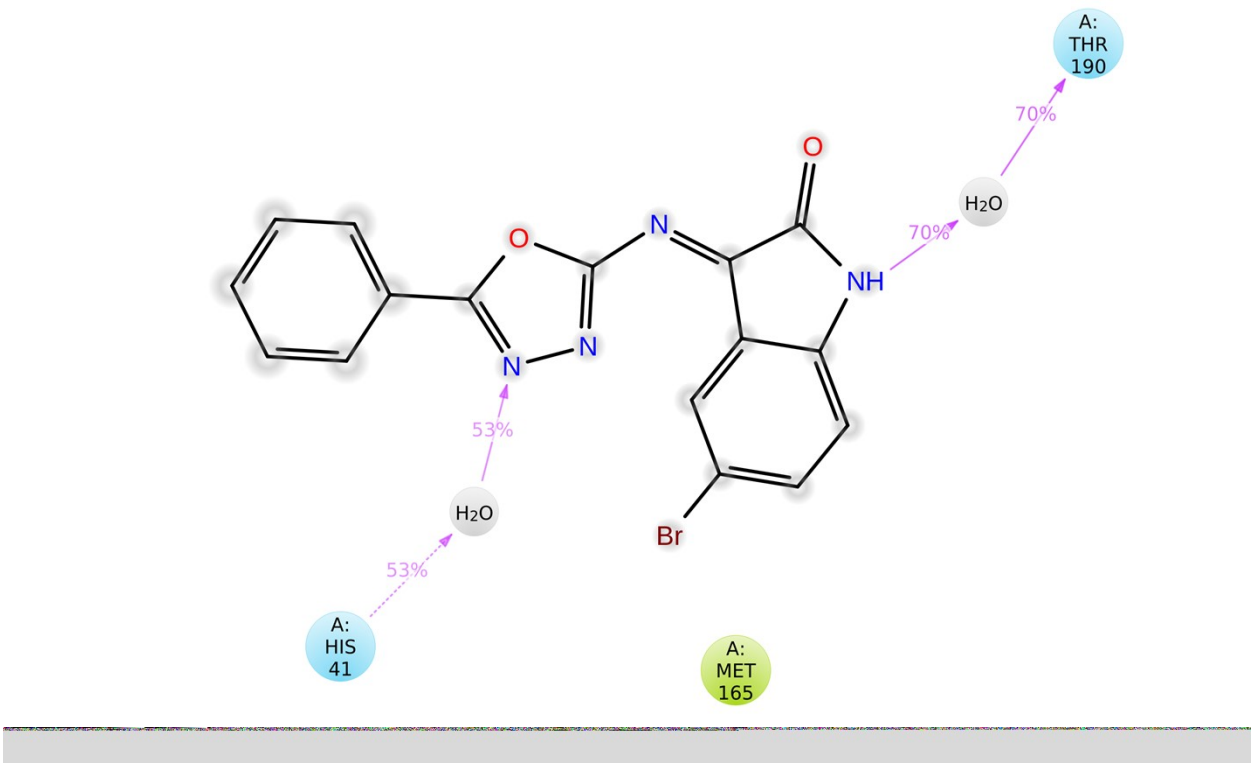


Figure SI12: The IV_e – 6LU7 Interactions that occur more than 30.0% of the simulation time.

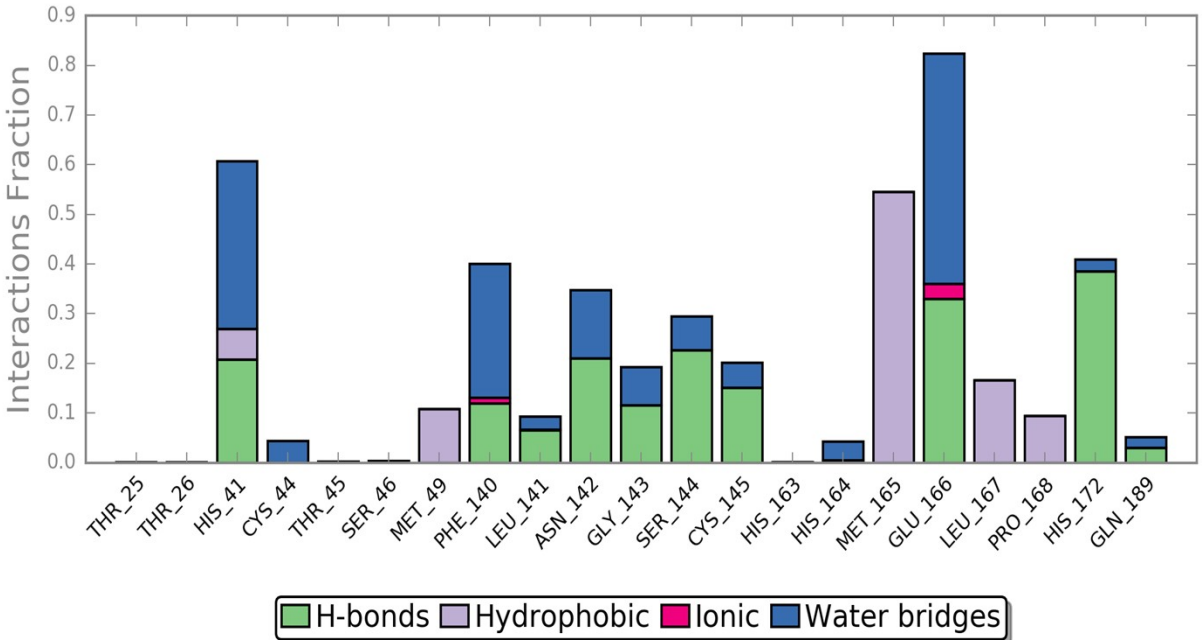


Figure SI13: The histogram of I_a – 6LU7 contact throughout the trajectory.

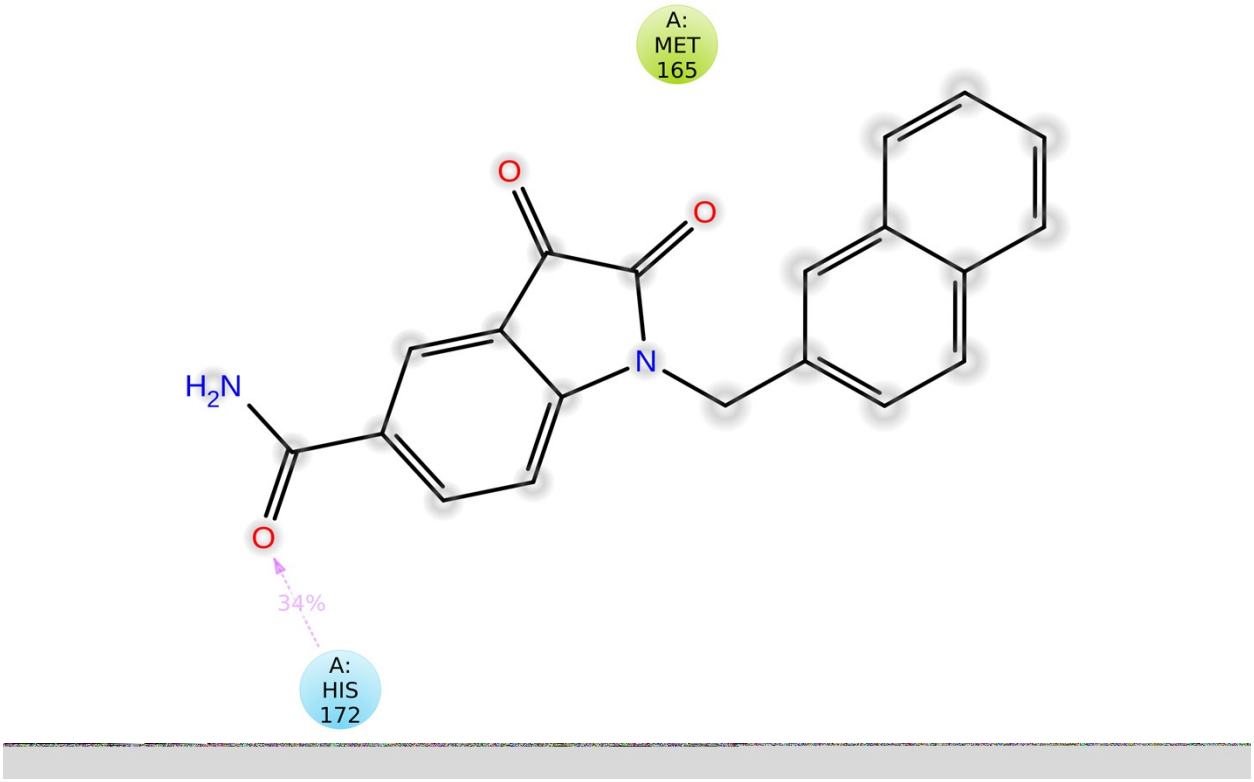


Figure SI14: The I_a – 6LU7 Interactions that occur more than 30.0% of the simulation time.