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Docking Analysis of 07 Anti-HCV Drugs with COVID-19 Main Protease PDB ID: 6LU7

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Abstract 07 anti-HCV drugs have been processed and observed by docking analysis for understanding the binding patteren of drugs with COVID-19 main protease PDB ID: 6LU7 for any possibilities of protease inhibition. For docking analysis PyRx- Python Prescription 0.8 was used. This analysis reveals that the essential amino acids involved in binding of anti-HCV drugs to COVID-19 main protease PDB ID: 6LU7 are Threonine (THR), Cysteine (CYS), Histidine (HIS), Methionine (MET) and Proline (PRO). After docking analysis it was observed that Ledipasvir may be act as COVID-19 main protease inhibitor despite of being anti-HCV and may further be used in the treatment of COVID-19 infection after having proper clinical proofs.

Keywords: *COVID-19, anti-HCV, protease inhibition*

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1. Introduction

Corona virus is well known threat peaking its crown again to world in the form of nCoV-19 (COVID-19) during the current time which was initially supposed to be emerged several years ago in different other forms like Middle East Respiratory Syndrome-Corona-Virus (MERS-CoV) and Severe Acute Respiratory Syndrome-corona-virus (SARS-CoV) with the few similar pathological symptoms but with great power of spreading infection to one another. [1] There is an option out of many for management of virus is known as inhibition of RNA dependent RNA protease (RdRp) enzyme in virus for cessation of viral replication. [2] Hence, to contribute a little with some possibilities of inhibition of RNA dependent RNA protease (RdRp) enzyme of COVID-19 virus by existing anti-HCV drugs; we have screened 7 anti-HCV drugs which were already approved and tested against their pharmacokinetic, pharmacodynamic and toxicity parameters; for studying their molecular interaction with recently deposited and released crystal structure of COVID-19 main protease (viral protein) with Protein Data Bank (PDB) ID: 6LU7. [3] The drug molecules which were used in this study are Daclatasvir (Hepatitis C virus (HCV) NS5A replication complex inhibitor) [4], Dasabuvir (It emerges as medical advance when used as a combination therapy for HCV) [5], Elbasvir [6], Ledipasvir [7], Lomibuvir [8], Ombitasvir [9] and Paritaprevir [10].

To study this interaction between pre-established anti-HCV drugs and crystal structure of COVID-19 main protease we have used docking analysis. [11,12,13,14]

2. Materials and Methods

2.1. Data, Database, and Tools

For carrying out this study, National Center for Bio-technology Information's (NCBI) website and Protein Data Bank's (PDB) website were used as biological and chemical data sources. For designing and optimizing the geometry of the derivatives, ChemDraw Ultra 10.0 [11,15]. Co-crystallized 3D structure of COVID-1 main protease; PDB ID: 6LU7 (viral protein) was downloaded from Protein Data Bank.

2.2. Docking

The docking analysis of 07 anti-HCV drugs and inhibitor N3 complexes within 3D structure of COVID-19 main protease; PDB ID: 6LU7 was performed by PyRx- Python Prescription 0.8.

PyRx is Virtual Screening software for Computational Drug Discovery that can be used to screen libraries of compounds against potential drug targets. PyRx enables Medicinal Chemists to run Virtual Screening from any platform and helps users in every step of this process - from data preparation to job submission and analysis of the results.

3. Results and Discussion

07 anti-HCV drug molecules were processed for virtual screening via docking studies. All the molecules were

analyzed for their binding characteristics such as binding residues (Amino Acid: AA), number of hydrogen bonds, binding atoms with type of bonds. All these observed characteristics are given in Table 1 to Table 16 and clicked photographs of molecular interactions are given in Figure 1.

Table 1. Daclatasvir- Hydrophobic Interactions

Index	Residue	AA	Distance	Ligand Atom	Protein Atom
1	5A	LYS	3.57	4735	67
2	126A	TYR	3.77	4739	1947
3	137A	LYS	3.53	4682	2127
4	237A	TYR	3.91	4715	3630
5	272A	LEU	3.89	4713	4159
6	286A	LEU	3.54	4689	4357
7	290A	GLU	3.57	4685	4421

Table 2. Daclatasvir- Hydrogen Bonds Interaction

Index	Residue	AA	Distance H-A	Distance D-A	Donor Angle	Protein donor?	Side chain	Donor Atom	Acceptor Atom
1	5A	LYS	3.13	3.94	136.17	✓	✓	71 [N3+]	4726 [O2]
2	127A	GLN	2.16	3.17	167.46	✓	✗	1961 [Nam]	4730 [O2]
3	127A	GLN	2.99	3.68	125.89	✗	✗	4719 [Npl]	1964 [O2]
4	239A	TYR	2.12	3.11	160.98	✓	✓	3669 [O3]	4705 [O2]
5	239A	TYR	2.44	3.40	156.09	✗	✓	4695 [Npl]	3669 [O3]

Table 3. Dasabuvir - Hydrophobic Interactions

Index	Residue	AA	Distance	Ligand Atom	Protein Atom
1	249A	ILE	3.76	4691	3822
2	249A	ILE	3.96	4695	3821
3	293A	PRO	3.69	4695	4470
4	294A	PHE	3.42	4683	4485
5	294A	PHE	3.68	4686	4483

Table 4. Dasabuvir -Hydrogen Bonds Interaction

Index	Residue	AA	Distance H-A	Distance D-A	Donor Angle	Protein donor?	Side chain	Donor Atom	Acceptor Atom
1	246A	HIS	2.73	3.48	132.83	✗	✓	4697 [Npl]	3779 [N2]

Table 5. Elbasvir -Hydrophobic Interactions

Index	Residue	AA	Distance	Ligand Atom	Protein Atom
1	294A	PHE	3.55	4683	4486

Table 6. Elbasvir -Hydrogen Bonds Interaction

Index	Residue	AA	Distance H-A	Distance D-A	Donor Angle	Protein donor?	Side chain	Donor Atom	Acceptor Atom
1	110A	GLN	2.33	3.15	135.98	✓	✓	1729 [Nam]	4684 [O3]
2	111A	THR	1.96	2.96	163.21	✓	✗	1738 [Nam]	4682 [O3]

Table 7. Ledipasvir -Hydrophobic Interactions

Index	Residue	AA	Distance	Ligand Atom	Protein Atom
1	5A	LYS	3.47	4718	69
2	5A	LYS	3.80	4719	67
3	137A	LYS	3.49	4687	2127
4	199A	THR	3.91	4724	3005
5	272A	LEU	3.83	4749	4159
6	276A	MET	3.92	4745	4213
7	286A	LEU	3.62	4730	4355
8	286A	LEU	3.48	4695	4357

Table 8. Ledipasvir -Hydrogen Bonds Interactions

Index	Residue	AA	Distance H-A	Distance D-A	Donor Angle	Protein donor?	Side chain	Donor Atom	Acceptor Atom
1	127A	GLN	2.80	3.72	150.03	✓	✗	1961 [Nam]	4715 [O3]
2	239A	TYR	2.23	3.19	154.04	✓	✓	3669 [O3]	4726 [Npl]
3	239A	TYR	2.62	3.19	115.39	✗	✓	4726 [Npl]	3669 [O3]
4	285A	ALA	1.90	2.84	154.97	✗	✗	4737 [Nam]	4344 [O2]
5	287A	LEU	2.84	3.85	168.61	✓	✗	4370 [Nam]	4728 [Npl]

Table 9. Lomibuvir -Hydrophobic Interactions

Index	Residue	AA	Distance	Ligand Atom	Protein Atom
1	218A	TRP	3.93	4682	3307
2	218A	TRP	3.81	4683	3309
3	270A	GLU	3.54	4686	4122
4	271A	LEU	3.59	4686	4140

Table 10. Lomibuvir- Hydrogen Bonds Interactions

Index	Residue	AA	Distance H-A	Distance D-A	Donor Angle	Protein donor?	Side chain	Donor Atom	Acceptor Atom
1	279A	ARG	2.84	3.22	102.75	✔	✔	4257 [Ng+]	4687 [O3]

Table 11. Ombitasvir- Hydrophobic Interactions

Index	Residue	AA	Distance	Ligand Atom	Protein Atom
1	169A	THR	3.84	4744	2594
2	171A	VAL	3.41	4747	2614
3	197A	ASP	3.88	4727	2977
4	239A	TYR	3.90	4701	3666
5	272A	LEU	3.81	4700	4159
6	286A	LEU	3.69	4698	4355
7	287A	LEU	3.77	4700	4376

Table 12. Ombitasvir - Hydrogen Bonds Interactions

Index	Residue	AA	Distance H-A	Distance D-A	Donor Angle	Protein donor?	Side chain	Donor Atom	Acceptor Atom
1	137A	LYS	2.18	3.12	150.73	✔	✔	2129 [N3+]	4731 [O2]
2	276A	MET	2.51	3.30	133.36	✔	✘	4209 [Nam]	4715 [O2]
3	277A	ASN	2.58	3.05	106.99	✔	✘	4226 [Nam]	4715 [O2]
4	278A	GLY	2.31	3.29	159.19	✔	✘	4240 [Nam]	4715 [O2]
5	285A	ALA	2.73	3.43	127.83	✘	✘	4713 [Nam]	4344 [O2]
6	287A	LEU	2.94	3.79	140.54	✔	✘	4370 [Nam]	4702 [Nam]

Table 13. Paritaprevir - Hydrophobic Interactions

Index	Residue	AA	Distance	Ligand Atom	Protein Atom
1	137A	LYS	3.58	4709	2125
2	171A	VAL	3.94	4736	2615
3	194A	ALA	3.74	4736	2946
4	238A	ASN	3.86	4686	3648
5	272A	LEU	3.78	4727	4159
6	286A	LEU	3.73	4713	4358

Table 14. Paritaprevir - Hydrogen Bonds Interactions

Index	Residue	AA	Distance H-A	Distance D-A	Donor Angle	Protein donor?	Side chain	Donor Atom	Acceptor Atom
1	137A	LYS	2.38	3.38	163.29	✔	✔	2129 [N3+]	4731 [O2]
2	197A	ASP	2.71	3.32	120.11	✘	✔	4729 [Nam]	2980 [O2]
3	197A	ASP	2.40	3.04	119.66	✘	✔	4738 [Nar]	2980 [O2]
4	239A	TYR	2.21	3.22	165.20	✔	✔	3669 [O3]	4720 [O2]
5	287A	LEU	2.18	3.18	162.58	✔	✘	4370 [Nam]	4725 [O2]

Table 15. N3 Reference molecule- Hydrophobic Interactions

Index	Residue	AA	Distance	Ligand Atom	Protein Atom
1	25A	THR	3.74	4713	353
2	26A	THR	3.88	4713	367
3	41A	HIS	3.77	4725	607
4	145A	CYS	2.80	4703	2236
5	165A	MET	3.81	4724	2527
6	168A	PRO	3.53	4681	2579

Table 16. N3 Reference molecule- Hydrogen Bond Interaction

Index	Residue	AA	Distance H-A	Distance D-A	Donor Angle	Protein donor?	Side chain	Donor Atom	Acceptor Atom
1	140A	PHE	3.62	4.03	108.21	✗	✗	4721 [O3]	2164 [O2]
2	140A	PHE	2.41	3.19	131.79	✗	✗	4719 [N3]	2164 [O2]
3	143A	GLY	1.96	2.87	145.15	✓	✗	2214 [Nam]	4707 [O3]
4	144A	SER	3.67	3.99	100.53	✓	✓	2226 [O3]	4721 [O3]
5	164A	HIS	1.81	2.80	161.30	✗	✗	4701 [Nam]	2509 [O2]
6	166A	GLU	1.97	2.98	164.27	✓	✗	2540 [Nam]	4696 [O2]
7	166A	GLU	1.83	2.83	162.94	✗	✗	4693 [Nam]	2543 [O2]
8	189A	GLN	1.95	2.89	149.82	✗	✓	4697 [Nam]	2881 [O2]
9	190A	THR	1.84	2.85	166.73	✗	✗	4689 [Nam]	2894 [O2]

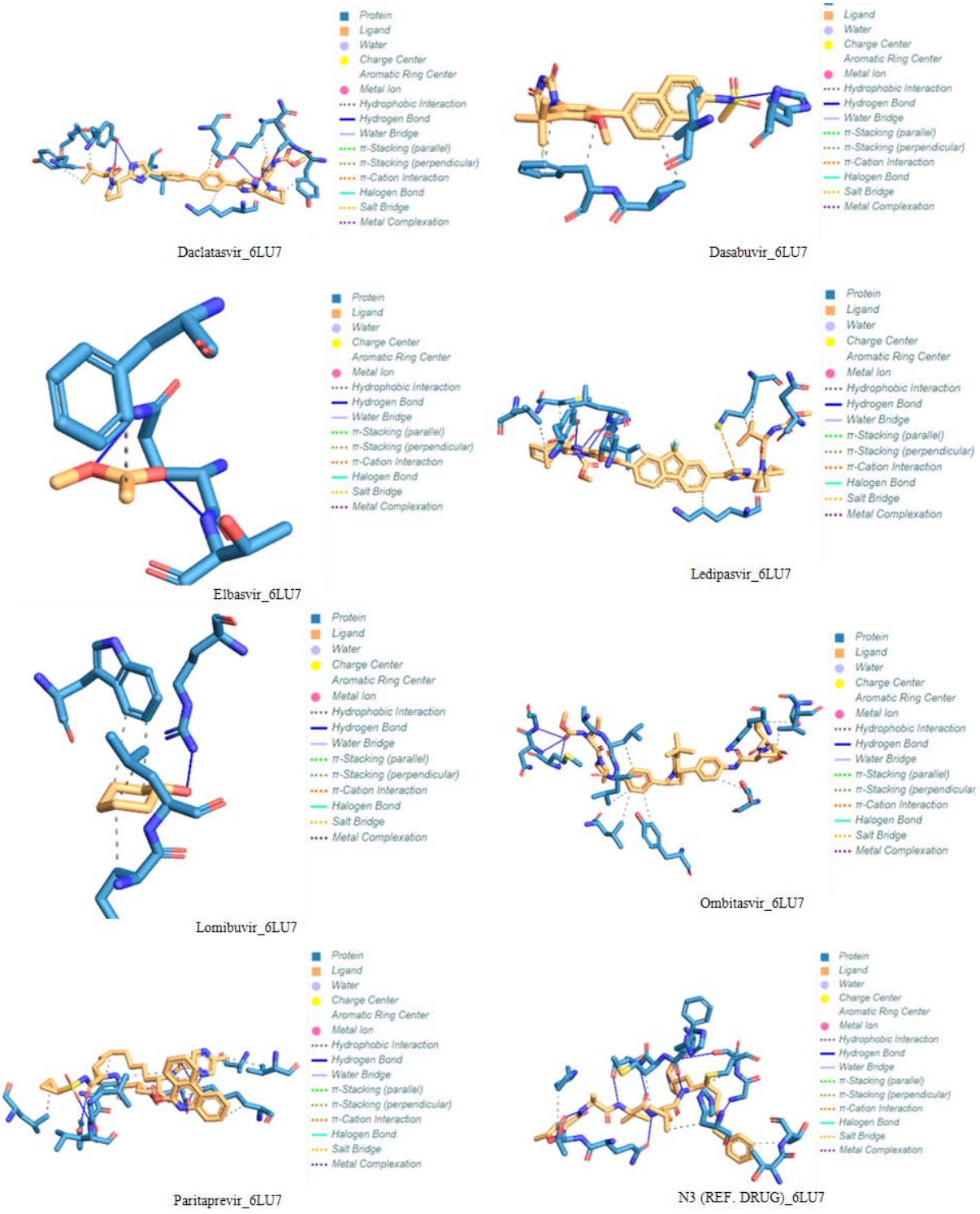

Figure 1. Docked images of anti-HCV drugs taken and ref. drug complexes in COVID-19 main protease 6LU7

Table 17. Residual analysis of docked anti-HCV drugs

Ligands	No. of Hydrogen Bonds	Essential Residues					No. of Residues matching with Ref. Molecule
N3 (Ref. molecule)	9	THR	HIS	CYS	MET	PRO	
Daclatasvir	5	-	-	-	-	-	00
Dasabuvir	1	-	-	-	-	PRO	01
Elbasvir	2	-	-	-	-	-	00
Ledipasvir	5	THR	-	-	MET	-	02
Lomibuvir	1	-	-	-	-	-	00
Ombitasvir	6	THR	-	-	-	-	01
Paritaprevir	5	-	-	-	-	-	00

Binding Amino acids analysis has been performed. This comparative analysis was performed with the residues of inhibitor N3 complexes within 3D structure of COVID-19 main protease; PDB ID: 6LU7. This analysis is given in Table 17.

On analyzing Table 17, it was observed that Amino acids or residues which plays key role in binding of reference molecule N3 are THR (Threonine), HIS (Histidine), CYS (Cystein), MET (Methionine) and PRO (Proline)

Anti-HCV drugs Dasabuvir (associated amino acid is- PRO; No. of hydrogen bonds- 1), Ledipasvir (associated amino acids are- THR & MET; No. of hydrogen bonds- 5) and Ombitasvir (associated amino acid is- THR; No. of hydrogen bonds- 6) were found to be very close to the binding pocket of protein 6LU7.

4. Conclusions

Ledipasvir has shown its possibilities of having inhibition of COVID-19 main protease enzyme; this enzyme is responsible for replication of virus in living body. To reach this conclusion we have completed a journey of docking analysis of 07 well known anti-HCV drugs with COVID-19 main protease PDB ID: 6LU7. Docking was performed with the help of PyRx- Python Prescription 0.8 and the results were observed and analyzed; which screened 3 (Dasabuvir, Ledipasvir and Ombitasvir) out of 07 anti-HCV drugs having possibilities of protease inhibition of virus. Further residual analysis showed that Ledipasvir may have probabilities of protease inhibition for cessation of viral replication as amino acids of binding pocket (THR & MET out of 5 amino acids) were similar to reference molecule N3 complexes within 3D structure of COVID-19 main protease 6LU7. These results primarily showed the possibilities only although clinical studies are still required to ascertain the findings.

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Conflicts of Interest

The authors declare no conflict of interest.

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