Iranian Journal of Pharmaceutical Sciences
2021: 17 (2): 87-104
www.ijps.ir

Original Article

In Silico Study of Five SARS CoV-2 Target Proteins on Known Drugs

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Abstract

COVID-19 is an infectious disease that started at the end of 2019 in China then became pandemic worldwide. A number of crystal structures of coronavirus proteins are available in the Protein Data Bank. In this paper, we reported results from the virtual screening of databases including 2701 FDA approved drugs against five known coronavirus protein targets. Our results showed a wide range of scores for different drugs of which some were predicted to be active against one or some of the proteins. Among all of the compounds with higher scores, tannic acid and cobicistat showed to be active against four and two of the studied proteins respectively. Tannic acid which was reported to be an antiviral and potent inhibitor of hepatitis C virus activity and cobicistat with anti- HIV activity might be useful for the cure of COVID-19. According to the results, we suggest more studies on these valuable potential drugs.

Keywords: Virtual screening, Coronavirus, Tannic acid, Cobicistat, COVID-19, SARS CoV-2.

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Cite this article as Jamshidi Z, Akaberi M, Hadizadeh F, *In Silico* Study of five SARS CoV-2 Target Proteins on Known Drugs, 2021, 17 (2): 87-104.

1. Introduction

After severe acute respiratory syndrome (SARS) in 2003 and Middle East Respiratory Syndrome (MERS) in 2012, coronavirus (2019-nCoV or SARS CoV-2), a new member of the family Coronaviridae was reported in Wuhan, China in late 2019 [1-4]. Coronaviruses have an unusual potential to change tropism [5]. This is especially illustrated over the last 15 years by the development of two zoonotic CoVs, SARS, and MERS [6]. The coronaviruses particularly SARS CoV-2 have quickly spread worldwide and caused a global concern [7]. These viruses not only can infect humans, but also many animal species [8]. According to World Health

Organization (WHO), the Coronaviruses have caused around 40.665.438 new cases of disease and 1. 121.843 deaths in the world by October 22th, 2020 [9]. The spike (S) protein, nucleocapsid (N) protein, membrane (M) protein, and the envelope (E) protein are the four main structures of proteins encoded by the coronaviral genome [10]. The Coronaviruses are enveloped Positive-stranded RNA viruses [3]. Also they have the largest RNA genome among known RNA viruses with 26 to 32 kilobases viewed like crown under the electronic microscope [11-13]. There are different types of CoVs with low and high pathogenic potentials. HCoV-229E, HCoVOC43, HCoV-NL63, and HCoV-HKU are low pathogenic viruses while SARS-CoV and MERS-CoV are among the most dangerous ones[14]. Respiratory and intestinal infections are common symptoms caused by coronaviruses. The CoVs are able to cause a broad range of illness severity from the mild common cold to acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) [1, 15, 16]. Fever, dry cough, fatigue, anorexia, myalgia, and dyspnea are common clinical symptoms of COVID-19 [17, 18]. Five- crystal structures of the coronavirus including 5R7Y, 5R81, 5R82 (main protease), 6YI3 (N-terminal RNA-domain of the SARS-CoV-2 nucleocapsid phosphoprotein), and 7BTF (SARS-CoV-2 RNA-dependent RNA polymerase) were chosen for this study. Despite the efforts of scientists to discover vaccines and anti-viral drugs for prevention or treatment of SARS CoV-2, there have not been significant successes so far since discovering drugs for a novel virus might take several years and need high cost to complete [19-21]. Thus, finding a treatment for this unknown disease is very necessary. In this research, we used a Virtual Screening (VS), a technique used for analyzing huge databases and discovering lead compounds, to find potential drugs among 2701 FDA approved drugs for the treatment of coronavirus [22-32].

2. Materials and Methods

In the current study, VS was used as a screening tool for predicting the efficacy of clinically approved drugs taken from the https://www.selleckchem.com/screening/fda-approved-drug-library.html , consisting of 2701 approved drugs with (SDF) format.

The Amber10: EHT Force Field and the default docking setting of the Molecular Operating Environment (MOE, Chemical Computing Group Inc.: Montreal, Http:// www.chemcomp/com) software was used. The placement method was Triangle Matcher and Refinement was done with Rigid Receptor with the scoring of London dG and GBVl/WSA dG respectively (Figure 1).

Five crystal structures of the SARS CoV-2 downloaded from RCSB PDB database (www.rcsb.org/structure), included 1- The crystal structure of complex SARS Cov-2 main protease with an inhibitor N3 (5R7Y), 2- crystal structure of complex SARS Cov-2 main protease with Z1367324110 (5R81), 3- crystal structure of complex SARS Cov-2 main protease with Z219104216 (5R82), 4- The N-terminal RNA-domain of the SARS-CoV-2 nucleocapsid phosphoprotein (6YI3),

and 5- SARS-CoV-2 RNA-dependent RNA polymerase in complex with cofactors in reduced condition (7BTF).

The x-ray co-crystalized ligand was used as active site in proteases (5R7Y, 5R81 and 5R82) and in case of two others Nucleocapsid (6YI3) and RNA polymerase (7BTF) site finder module of MOE was used to find active site for docking study. Validation of docking method was performed through docking of co-crystallized ligands in proteases and finding its RMSD value which was less than $2A^{o}$.

3. Result and Discussion

Ten clinically approved drugs with the highest scorings in this study are listed in Tables 1, 4, 7, 10, and 13. Tables were sorted according to binding affinity (binding free energy kcal/mol).

3.1. 5R7Y

The screening result for 5R7Y protease is shown in table 1. Lypressin acetate had the highest score among the listed drugs. Lypressin acetate is a hormone nonapeptide, so it is a substrate for protease [33]. Even if it bound to the target, it would be immediately cleaved by the target itself, so it is not an appropriate drug for SARS Cov-2 main protease. Growth Hormone Releasing Peptide-2 (GHRP-2) and thymopentin (an immune stimulant) are also peptides; therefore, they cannot be used as a potential drug. Delamanid is an anti-tuberculosis agent derived from the nitro dihydroimidazooxazole class of compounds that are used to treat multidrug-resistant tuberculosis [34]. Tannic acid has a diversity of biological effects. Tannins, naturally or synthetically gained noticeable effectiveness against a huge range of viruses including herpes simplex and hepatitis C, human immunodeficiency , adenoviruses, and influenza virus A. *In vitro* study also exhibited antioxidant properties Tannins bound to virus-specific proteins and they work as competitors for glycosaminoglycans in the treatment of herpes simplex infections [35-44]. Among the drugs checked out, tannic acid and delamanid may have the potential to be used for the treatment of coronavirus disease. The interactions between (tannic acid + 5R7Y) and (delamanid + 5R7Y) were shown in Figures ٢ and ٣. In tables 2 and 3, ligand interactions between (tannic acid + 5R7Y) and (delamanid + 5R7Y) were illustrated.

3.2. 7BTF

The screening result for 7BTF RNA polymerase was shown in table 4. Nafarelin acetate had the highest score among the listed drugs. Nafarelin acetate is a synthetic agonist of gonadotropin-releasing hormone that is used for endometriosis[45]. Daptomycin is a lipopeptide antibiotic used in the treatment of systemic and life-threatening problems [46]. Cobicistat is used for the treatment of HIV/AIDS virus infection (HIV/AIDS) [47]. Iodixanol is an iodine-containing non-ionic radiocontrast agent that is commonly used as a contrast agent during coronary angiography[48] . Among the drugs checked out, tannic acid and cobicistat might have the potential to be used for treating coronavirus disease. The interactions between (tannic acid

+ 7BTF) and (cobicistat + 7BTF) were shown in figures ٤ and ٥. In tables 5 and 6, ligand interactions report between (tannic acid + 7BTF) and (cobicistat + 7BTF) were shown.

3.3. 6YI3

In table 7, screening result for 6YI3 nucleocapsid phosphoprotein was presented. As can be observed, tannic acid has the highest affinity. Elbasvir is a complex organic heterotetracyclic compound used for treating hepatitis C virus [49]. Vancomycin is an antibiotic used to treat a number of bacterial infections[50]. Terlipressin is an analog of vasopressin used as a vasoactive drug in the management of hypotension which has been found to be effective when norepinephrine fails [51]. Among the drugs checked out, tannic acid and elbasvir could have the potential to treat coronavirus disease. The interactions between (tannic acid + 6YI3) and (elbasvir + 6YI3) were shown in figures ٦ and ٧. In tables 8 and 9, ligand interactions report between (tannic acid + 6YI3) and (elbasvir + 6YI3) were listed.

3.4. 5R81

The screening result for 5R81 protease is shown in table 10. Tannic acid had the highest score in the table. Mirabegron is in a class of medications called beta-3 adrenergic agonists that are used to treat overactive bladder. It works by relaxing the bladder muscles to prevent urgent, frequent, or uncontrolled urination [52]. Asunaprevir is an inhibitor of the hepatitis C virus enzyme serine protease NS3[53]. Haloperidol is used in the treatment of schizophrenia, tics in Tourette syndrome, mania in bipolar disorder, nausea and vomiting, delirium, agitation, acute psychosis, and hallucinations in alcohol withdrawal[54]. Chlorhexidine is one of the most common skin and mucous membrane antiseptic [55]. Among the drugs checked out, tannic acid and asunaprevir may have the potential to treat coronavirus disease. The interactions between (tannic acid + 5R81) and (asunaprevir + 5R81) were shown in figures ٨ and ٩. In tables 11 and 12, ligand interactions report between (tannic acid + 5R81) and (asunaprevir + 5R81) were depicted.

3.5. 5R82

The screening result for 5R82 protease is shown in table 13. Atosiban acetate showed the highest score in the table. It is an inhibitor of the hormones oxytocin and vasopressin and used for the delay of imminent preterm birth in pregnant women [56]. Teniposide is an antitumor agent that inhibits DNA synthesis. Teniposide has common side effects including bone marrow, suppression of gastrointestinal toxicity, hypersensitivity reactions, and reversible alopecia [57]. Teniposide is not an appropriate drug for the treatment of COVID-19 because of its dangerous side effects. Telaprevir is a pharmaceutical drug for the treatment of hepatitis C. It is a member of a class of antiviral drugs known as protease inhibitors [58]. Among the drugs checked out, telaprevir and cobicistat could have the potential to treat coronavirus disease. The interactions between (telaprevir + 5R82) and (cobicistat + 5R82) were depicted in figures 10

and 11. In tables 14 and 15, ligand interactions report between (telaprevir + 5R82) and (cobicistat + 5R82) were shown.

4. Conclusion

The study suggested that tannic acid and cobicistat might be potent drugs for wet-lab studies in the treatment of COVID-19. Tannic acid is a plant-derived polyphenol that could be a potential candidate for the evolution of antiviral drugs. Tannic acid was effective on four SARS-CoV-2 target proteins (PDB codes: 5R7Y, 7BTF, 6YI3, 5R81). Cobicistat, used in the treatment of virus infection (HIV/AIDS), was predicted to be effective on two SARS-CoV-2 target proteins (7BTF, 5R82). Further studies for investigating the clinical efficacy of these two drugs are highly recommended.

Acknowledgments

The authors are thankful to Mashhad University of Medical Sciences (Mashhad, Iran) for the financial support (grant no. 990240).

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Tables:

Table 1. Result of the VS on the crystal structure of COVID-19 main protease (5R7Y).

Approved drug	Formula	Molweight	Affinity	s	Mechanism of action	rmsd-refine	E-conf	E-place	E-score 1	E-refine
Lypressin Acetate	C46H65N13O1252	1056.23	-11.79	-7.88	Vasopressin via receptor	3.96	-48.36	-43.11	-6.29	-44.31
*Tannic acid	C76H52O46	1701.20	-11.06	-7.65	bleeding, chronic diarrhea, dysentery, bloody urine, painful joints, persistent coughs, and cancer.	5.21	25.07	-71.23	-11.78	-50.42
*Delamanid	C25H25F3N4O6	534.49	-10.35	-8.53	Anti- tuberculosis	2.30	71.35	-85.81	-11.63	-48.52
Thymopentin	C30H49N9O9	679.77	-9.89	-7.64	Immunology & Inflammation related	2.07	-214.87	-63.98	-9.83	-42.17
Zofenopril calcium	C44H44CaN2O8S4	897.17	-9.86	-8.17	Angiotensin converting enzyme inhibitor	3.82	4.76	-50.82	-6.48	-47.47
GHRP-2	C42H50N8O5	746.90	-9.14	-7.83	Growth Hormone Releasing Peptide	2.33	32.41	-79.69	-9.96	-40.35
Bimatoprost	C25H37NO4	415.56	-9.10	-8.25	Prostaglandin F_2-alpha receptor agonist	1.23	-41.72	-82.92	-9.88	-36.66
Mycophenolate mofetil	C23H31NO7	433.49	-9.03	-7.85	Inosin-5-monophosphate dehydrogenase1 inhibitor	1.70	65.64	-83.20	-10.26	-38.31
Lercanidipine	C36H41N3O6	611.72	-8.90	-7.98	Voltage dependent calcium channel gamma-1 subunit inhibitor	1.74	25.83	-66.61	-9.13	-43.65
Sofalcone	C27H30O6	450.52	-8.64	-7.75	Anti -bacterial	1.16	6.40	-65.53	-11.77	-44.25

Affinity – (binding free energy) (kcal/ mol)Score; (S: the final score of GBVI/WSA binding free energy) (kcal/ mol); RMSD_refine – the mean square deviation after refinement; E_conf– energy conformer; E_place – score of the placement phase; E_scor1 – score the first step of notation; E_refine – score refinement;. *Drug with the lowest S score

Table 2. Ligand Interactions Report (5R7Y+Tannic acid).

Ligand	Receptor	Interaction	Distance	E (kcal/mol)
O 65	OG SER 10 (A)	H-donor	2.71	-2.6
O 114	O SER 1 (A)	H-donor	2.74	-3.0
O 135	O VAL 303 (A)	H-donor	2.68	-3.5
O 151	O HOH 15	H-donor	2.70	-1.7
O 153	SD MET 6 (A)	H-donor	3.18	-2.1
O 158	OE1 GLU 14 (A)	H-donor	2.56	-4.4
O 164	O CYS 300 (A)	H-donor	2.64	-3.0
O 166	OE1 GLU 14 (A)	H-donor	2.55	-1.2
O 171	O HOH 11	H-donor	2.68	-2.4
O 91	O HOH 16	H-acceptor	2.68	-2.3
O 96	N GLY 11 (A)	H-acceptor	2.92	-2.1
6-ring	CA PRO 9 (A)	pi-H	3.88	-0.5

Table 3. Ligand Interactions Report (5R7Y+ Delamanid).

Ligand	Receptor	Interaction	Distance	E (kcal/mol)
N 53	N SER 1 (A)	H-acceptor	3.02	-7.1
F 56	N MET 6 (A)	H-acceptor	3.04	-0.5
O 58	ND2 ASN 214 (A)	H-acceptor	2.96	-1.4
O 58	SG CYS 300 (A)	H-acceptor	3.14	-0.7
C 9	6-ring PHE 8 (A)	H-pi	3.68	-0.7

Table 4. Result of the VS on the crystal structure of SARS-CoV-2 RNA-dependent RNA polymerase (7BTF).

Approved drug	Formula	Molweight	Affinity	s	Mechanism of action	rmsd - refine	E-conf	E-place	E-score 1	E-refine
Nafarelin Acetate	C66H83N17O13	1322.47	-15.69	-10.03	Gonadotropin releasing hormone	2.21	-155.54	-67.51	-9.75	-5.53
Daptomycin	C72H101N17O26	1620.67	-13.82	-10.26	Lipopeptide antibiotic	2.85	-246.63	-26.55	-8.20	-62.19
Alarelin Acetate	C56H78N16O12	1167.32	-13.60	-8.93	GnRH agonist	4.89	-139.99	-71.57	-6.78	-47.29
*Tannic Acid	C76H52O46	1701.20	-12.98	-9.82	bleeding, chronic diarrhea, dysentery, bloody urine, painful joints, persistent coughs, and cancer.	4.22	43.94	-58.45	-15.69	-60.34
Iodixanol	C35H44I6N6O15	1550.18	-11.35	-8.82	Iodine compounds attenuate x-ray	1.77	-3.61	-76.30	-11.81	-52.73
*Cobicistat	C40H53N7O552	776.02	-11.08	-9.23	Immunodeficiency P450/virus	1.29	-66.09	-18.00	-10.18	-45.80
Deforolimus	C53H84NO14P	990.21	-10.95	-9.96	Inhibits the mammalian target of rapamycin(mTOR)	2.69	198.57	-94.87	-12.56	-50.22
Anidulafungin	C58H73N7O17	1140.24	-10.78	-8.91	Anti-infection	5.31	133.65	-13.50	-2.59	-55.94
Lapatinib Freebase	C29H26ClFN4O4S	581.06	-10.72	-8.86	EGFR, HER2 Anti- cancer	3.18	29.23	-87.47	-12.20	-47.92
Thymopentin	C30H49N9O9	679.76	-10.54	-9.27	Immunology & Inflammation related	1.79	-220.34	-109.78	-13.35	-63.65

Affinity – (binding free energy) (kcal/ mol)Score; (S: the final score of GBVI/WSA binding free energy) (kcal/ mol); RMSD_refine – the mean square deviation after refinement; E_conf– energy conformer; E_place – score of the placement phase; E_scor1 – score the first step of notation; E_refine – score refinement;. *Drug with the lowest S score

Table 5. Ligand Interactions Report (7BTF+Tannic acid).

Ligand	Receptor	Interaction	Distance	E (kcal/mol)
C 5	O GLY 220 (A)	H-donor	3.36	-1.3
O 59	O TYR 38 (A)	H-donor	2.68	-4.6
O 99	O HOH 317	H-donor	2.66	-1.9
O 114	O HOH 321	H-donor	2.69	-2.7
O 135	O GLY 203 (A)	H-donor	2.74	-1.6
O 140	O ASP 36 (A)	H-donor	2.64	-2.2
O 142	OD1 ASP 221 (A)	H-donor	2.55	-1.6
O 149	O HOH 325	H-donor	2.68	-2.5
O 156	OD2 ASP 208 (A)	H-donor	2.65	-5.7
O 164	O HOH 325	H-donor	2.69	-2.7
O 166	OD2 ASP 208 (A)	H-donor	2.59	-6.0
O 171	O HOH 324	H-donor	2.68	-2.5
O 23	O HOH 276	H-acceptor	2.88	-2.2
O 35	OG1 THR 76 (A)	H-acceptor	2.81	-1.1
O 54	O HOH 326	H-acceptor	2.70	-1.5
O 102	O HOH 324	H-acceptor	2.78	-1.0
O 108	NZ LYS 73 (A)	H-acceptor	2.79	-8.8
O 114	O HOH 317	H-acceptor	2.75	-0.8

Table 6. Ligand Interactions Report (7BTF+ Cobicistat).

Ligand	Receptor	Interaction	Distance	E (kcal/mol)
C 50	6-ring PHE 35 (A)	H-pi	3.53	-0.7
6-ring	CD LYS 50 (A)	pi-H	3.56	-0.5
5-ring	6-ring PHE 48 (A)	pi-pi	3.67	-0.0

Table 7. Result of the VS on the crystal structure of N-terminal RNA-domain of the SARS-CoV-2 nucleocapsid phosphoprotein (6YI3).

Approved drug	Formula	Molweight	Affinity	s	Mechanism of action	rmsd-refine	E-conf	E-place	E-score1	E-refine
*Tannic acid	C76H52O46	1701.20	-14.90	-10.34	bleeding, chronic diarrhea, dysentery, bloody urine, painful joints, persistent coughs, and cancer.	3.195	55.23	-103.11	-12.29	-69.98
Vancomycin	C66H75Cl2N9O24	1449.25	-14.06	-9.86	Anti-infection	5.11	183.80	-91.41	-12.49	-66.00
Terlipressin Acetate	C52H74N16O15S2	1227.37	-12.79	-9.22	5-alpha Reductase	1.14	-23.32	-70.83	-10.06	-50.80
Alarelin Acetate	C56H78N16O12	1167.32	-11.92	-9.20	GnRH agonist	1.89	-164.86	-64.24	-7.00	-55.50
Bacitracin	C65H101N17O165	1408.67	-11.77	-8.75	Anti-infection	2.66	-10.67	-79.26	-7.76	-52.92
Nafarelin Acetate	C66H83N17O13	1322.47	-11.55	-8.72	Gonadotropin releasing hormone receptor agonist	1.81	-176.87	-92.07	-9.97	-54.90
*Elbasvir	C49H55N9O7	882.02	-11.37	-9.55	HCV protease	3.12	61.38	-72.09	-9.18	-60.04
Thymopentin	C30H49N9O9	679.76	-11.26	-8.97	Immunology & Inflammation related	2.24	-221.75	-101.26	-10.32	-53.05
Anidulafungin	C58H73N7O17	1140.32	-11.08	-8.87	Anti-infection	1.65	108.25	-83.02	-11.76	-52.09
Zofenopril calcium	C44H44CaN2O8S4	897.17	-10.32	-8.41	Angiotensin converting enzyme inhibitor	2.17	-1.63	-57.08	-9.51	-51.52

Affinity – (binding free energy) (kcal/ mol)Score; (S: the final score of GBVI/WSA binding free energy) (kcal/ mol); RMSD_refine – the mean square deviation after refinement; E_conf– energy conformer; E_place – score of the placement phase; E_scor1 – score the first step of notation; E_refine – score refinement;. *Drug with the lowest S score

Table 8. Ligand Interactions Report (6YI3+Tannic acid).

Ligand	Receptor	Interaction	Distance	E (kcal/mol)
O 73	O HOH 24	H-donor	2.79	-2.3
O 82	O ALA 112 (A)	H-donor	2.82	-3.3
O 87	O THR 51 (A)	H-donor	2.75	-1.1
O 92	OD1 ASN 110 (A)	H-donor	2.68	-3.9
O 133	OE1 GLU 134 (A)	H-donor	2.67	-1.7
O 149	O HOH 32	H-donor	2.68	-2.3
O 151	O HOH 27	H-donor	2.76	-2.4
O 153	OE1 GLU 134 (A)	H-donor	2.56	-5.1
O 158	OD1 ASN 113 (A)	H-donor	2.65	-3.6
O 164	O HOH 27	H-donor	2.69	-2.7
O 171	O HOH 31	H-donor	2.66	-2.5
O 54	ND2 ASN 8 (A)	H-acceptor	2.84	-2.7
O 91	N ALA 116 (A)	H-acceptor	2.91	-4.7
O 91	O HOH 20	H-acceptor	2.85	-0.9
O 99	O HOH 13	H-acceptor	2.77	-1.0
O 102	NH1 ARG 52 (A)	H-acceptor	2.77	-1.5
O 108	N ALA 112 (A)	H-acceptor	3.07	-3.6

Table 9. Ligand Interactions Report (6YI3+ Elbasvir).

Ligand	Receptor	Interaction	Distance	E (kcal/mol)
N 80	O HOH 19	H-donor	3.12	-2.1
O 33	O HOH 13	H-acceptor	2.75	-2.8
O 44	NH2 ARG 48 (A)	H-acceptor	2.78	-5.3
O 98	O HOH 19	H-acceptor	2.69	-0.7
O 114	OH TYR 69 (A)	H-acceptor	2.63	-3.0
6-ring	CA ASN 8 (A)	pi-H	3.99	-0.5

Table 10. Result of the VS on the crystal structure of COVID-19 main protease(5R81).

Approved drug	Formula	Molweight	Affinity	s	Mechanism of action	rmsd-refine	E-conf	E-place	E-score 1	E-refine
*Tannic acid	C76H52O46	1701.20	-10.88	-23.03	bleeding, chronic diarrhea, dysentery, bloody urine, painful joints, persistent coughs, and cancer.	4.79	42.17	-109.95	-16.39	-279.00
chlorhexidine	C22H32Cl4N10	578.37	-10.25	-22.52	anti-infection	1.59	-495.32	-78.38	-12.64	-334.27
Terlipressin Acetate	C52H74N16O15S2	1227.37	-9.73	-23.56	5-alpha Reductase	1.51	-27.15	-104.10	-12.02	-161.10
Bacitracin	C65H101N17O16S	1408.67	-8.77	-23.22	anti-infection	1.60	-19.16	-37.36	-4.75	-286.50
Acemetacin	C21H18ClNO6	415.82	-8.38	-22.78	COX	1.57	68.18	-33.16	-15.25	-173.05
Mirabegron	C21H24N4O25	396.511	-8.33	-22.97	Adrenergic Receptor	2.14	-26.43	-22.02	-12.34	-378.68
*Asunaprevir	C35H46ClN5O95	748.28	-7.51	-23.12	Hepatitis c virus enzyme serine protease NS	2.67	80.46	-16.59	-8.95	-267.50
Iopamidol	C17H22I3N3O8	777.08	-7.14	-24.49	Radiopaque contrast agents	1.64	20.49	-77.90	-11.44	-411.23
Salvianolic acid	C36H30O16	718.61	-6.94	-22.52	anti-oxidative	2.69	-52.13	-60.94	-18.22	-345.44
Haldol	C21H23ClFNO2	375.86	-5.57	-23.26	Dopamine Receptor	2.136	-8.74	-51.95	-11.37	-81.03

Affinity – (binding free energy) (kcal/ mol)Score; (S: the final score of GBVI/WSA binding free energy) (kcal/ mol); RMSD_refine – the mean square deviation after refinement; E_conf– energy conformer; E_place – score of the placement phase; E_scor1 – score the first step of notation; E_refine – score refinement;. *Drug with the lowest S score

Table 11. Ligand Interactions Report (5R81+Tannic acid).

Ligand	Receptor	Interaction	Distance	E (kcal/mol)
O 82	O HOH 6	H-donor	2.74	-2.7
O 87	O HOH 10	H-donor	2.67	-2.7
O 92	O SER 46 (A)	H-donor	2.83	-3.5
O 99	O THR 24 (A)	H-donor	2.76	-4.1
O 133	O HOH 9	H-donor	2.68	-1.9
O 142	O HOH 22	H-donor	2.68	-2.5
O 149	OD1 ASN 142 (A)	H-donor	2.67	-2.2
O 156	OE2 GLU 47 (A)	H-donor	2.57	-3.2
O 160	O HOH 22	H-donor	2.66	-2.7
O 166	OE2 GLU 47 (A)	H-donor	2.57	-3.1
O 171	OE2 GLU 166 (A)	H-donor	2.56	-3.4
O 173	O PRO 168 (A)	H-donor	2.75	-3.4
O 23	O HOH 11	H-acceptor	2.78	-0.8
O 35	OG1 THR 25 (A)	H-acceptor	2.74	-2.1
O 54	O HOH 13	H-acceptor	2.83	-1.9
O 96	O HOH 11	H-acceptor	2.84	-2.0

O 102	N GLY 143 (A)	H-acceptor	2.93	-3.6
6-ring	CA GLU 47 (A)	pi-H	4.23	-0.5

Table 12. Ligand Interactions Report (5R81+ Asunaprevir).

Ligand	Receptor	Interaction	Distance	E (kcal/mol)
C 6	OE1 GLU 47 (A)	H-donor	3.34	-0.5
N 38	OE2 GLU 47 (A)	H-donor	2.82	-5.2
O 72	O HOH 36	H-acceptor	2.70	-1.8
O 88	O HOH 36	H-acceptor	2.83	-1.9

Table 13. Result of the VS on the crystal structure of COVID-19 main protease (5R82).

Approved drug	Formula	Molweight	Affinity	s	Mechanism of action	rmsd-refine	E-conf	E-place	E-score 1	E-refine
Atosiban Acetate	C43H67N11O12S2	994.19	-11.87	-10.01	Oxytocin receptor antagonist	1.80	-30.19	-79.49	-10.61	-59.54
Thymopentin	C30H49N9O9	679.76	-10.80	-8.74	Immunology & Inflammation related	1.77	-219.73	-108.22	-13.52	-58.83
Monomethyl Auristatin E	C39H67N5O7	717.98	-10.57	-9.28	Microtubule Inhibition	1.32	146.45	-83.23	-10.99	-38.93
*Telaprevir	C36H53N7O6	679.85	-10.31	-8.46	HCV Protease	1.84	-290.54	-73.66	-11.54	-50.91
Nafarelin Acetate	C66H83N17O13	1322.47	-10.17	-8.69	Gonadotropin releasing hormone receptor agonist	2.34	-170.19	-41.56	-8.28	-56.64
Teniposide	C32H32O13S	656.65	-9.86	-8.78	Topoisomerase	1.27	118.89	-118.06	-15.08	-52.17
*Cobicistat	C40H53N7O5S2	776.02	-9.65	-8.81	P450	2.24	-59.43	-39.04	-10.20	-49.51
Eptifibatide Acetate	C35H49N11O9S20	831.69	-9.53	-8.95	Integrin beta-3	1.55	-250.95	-91.52	-12.05	-52.18
Salvianolic Acid	C36H30O16	718.61	-9.47	-8.49	anti-oxidative	1.74	-60.73	-124.03	-16.56	-52.48
Lypressin Acetate	C46H65N13O12S2	1056.22	-9.02	-8.79	Vasopressin via receptor	2.24	-58.18	-59.24	-11.19	-52.39

affinity – (binding free energy) (kcal/ mol)Score; (S: the final score of GBVI/WSA binding free energy) (kcal/ mol); RMSD_refine – the mean square deviation after refinement; E_conf– energy conformer; E_place – score of the placement phase; E_scor1 – score the first step of notation; E_refine – score refinement;. *Drug with the lowest S score

Table 14. Ligand Interactions Report (5R82+ Telaprevir).

Ligand	Receptor	Interaction	Distance	E (kcal/mol)
N 38	O HOH 53	H-donor	2.92	-2.8
N 55	OD1 ASN 142 (A)	H-donor	3.03	-2.1
N 61	OD1 ASN 142 (A)	H-donor	2.93	-0.7
O 35	O HOH 53	H-acceptor	2.91	-0.5
O 37	OG SER 46 (A)	H-acceptor	2.66	-2.5
O 51	O HOH 59	H-acceptor	2.75	-2.9
O 58	O HOH 51	H-acceptor	2.79	-2.2
O 64	N GLU 166 (A)	H-acceptor	3.02	-1.9
N 71	NE2 HIS 163 (A)	H-acceptor	3.09	-4.4

Table 15. Ligand Interactions Report (5R82+ Cobicistat).

Ligand	Receptor	Interaction	Distance	E (kcal/mol)
N 17	O HOH 66	H-donor	2.94	-2.5
N 45	OD1 ASN 142 (A)	H-donor	3.40	-0.6
O 13	O HOH 59	H-acceptor	2.82	-2.5
O 13	O HOH 63	H-acceptor	2.64	-1.1
5-ring	CA THR 25 (A)	pi-H	3.84	-0.5
5-ring	CB ASN 142 (A)	pi-H	3.72	-0.5

Figures:

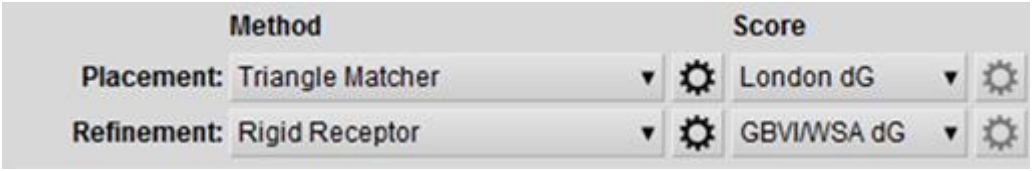

Figure 1. representation of Docking setting used in MOE software.

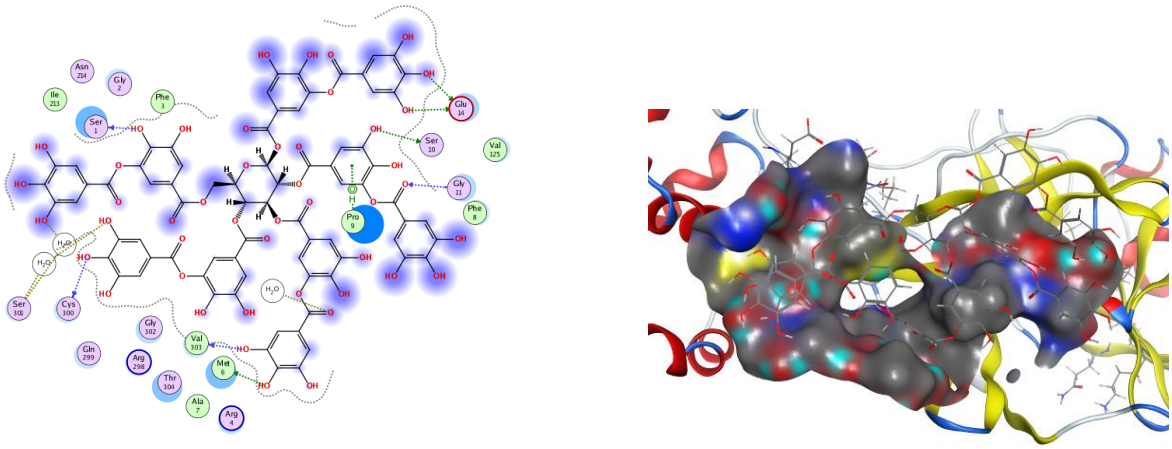

Figure 2. (5R7Y+Tannic acid).

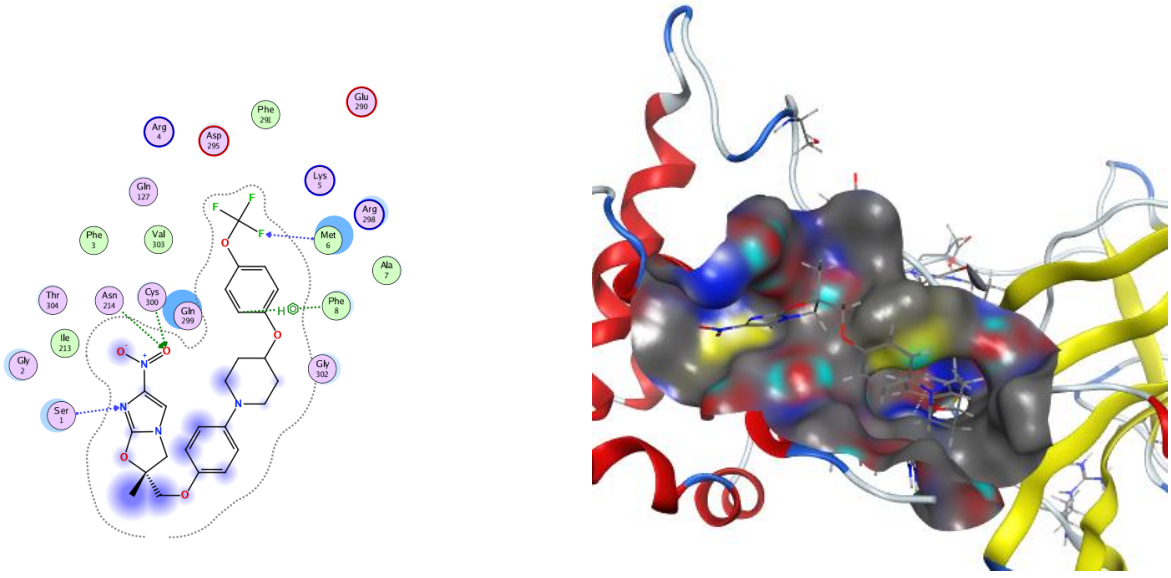

Figure 3. (5R7Y+ Delamanid).

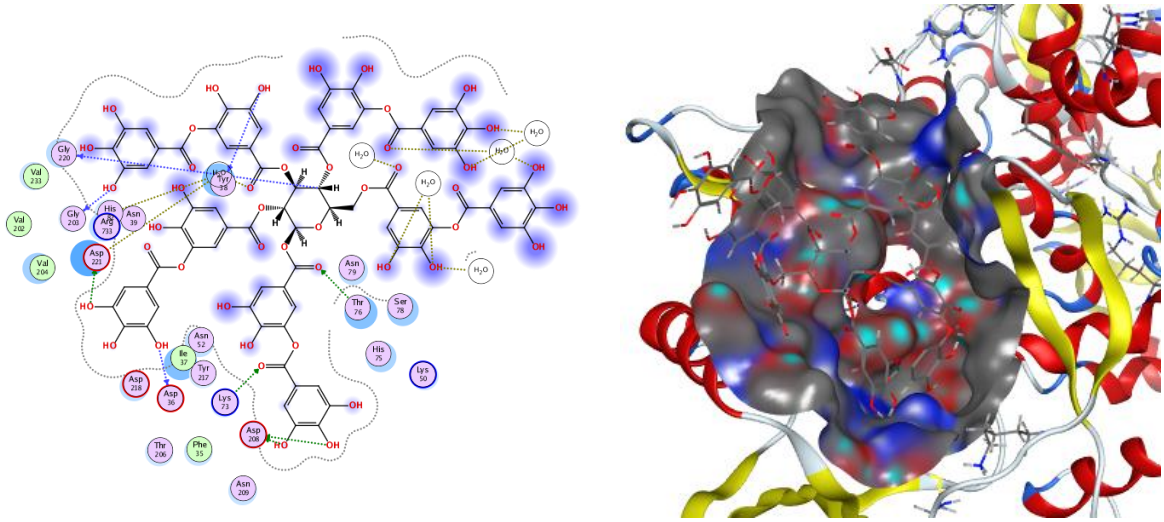

Figure 4. (7BTF+Tannic acid).

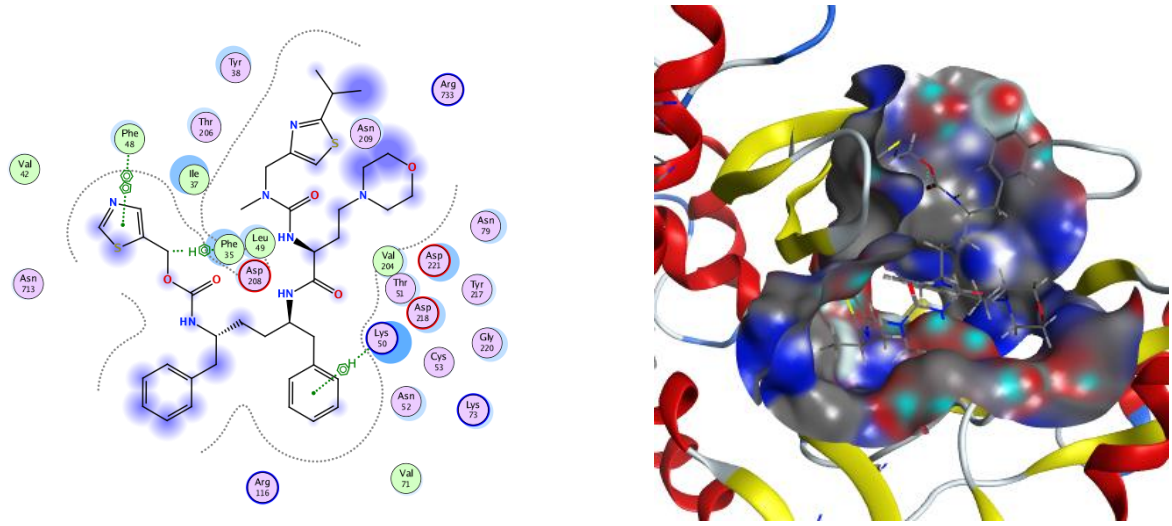

Figure 5. (7BTF+ Cobicistat).

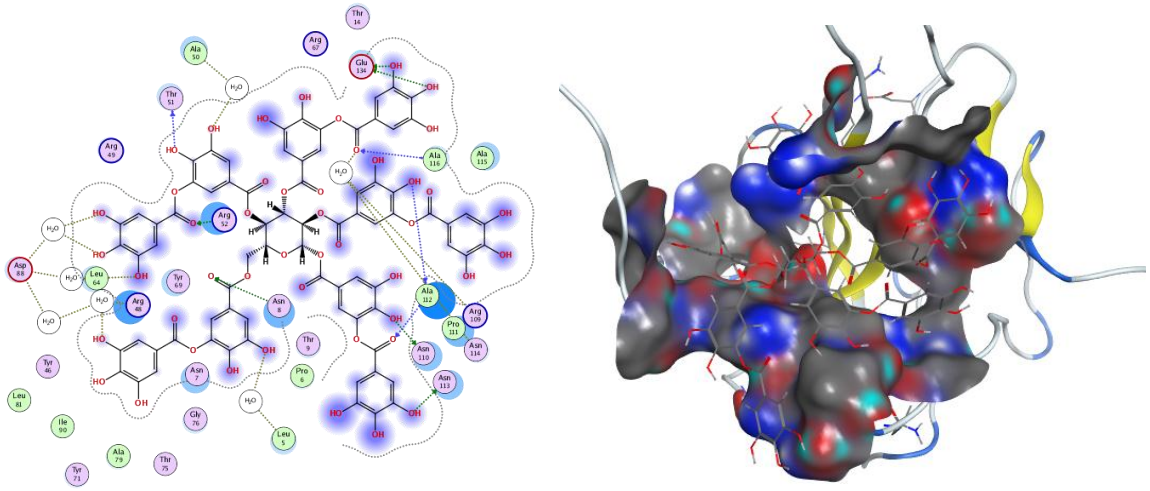

Figure 6. (6YI3+Tannic acid).

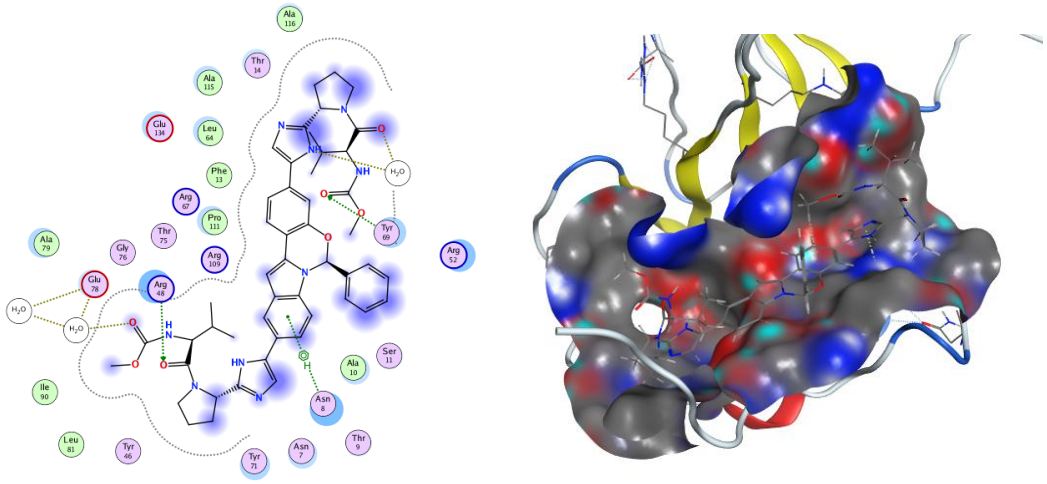

Figure 7. (6YI3+ Elbasvir).

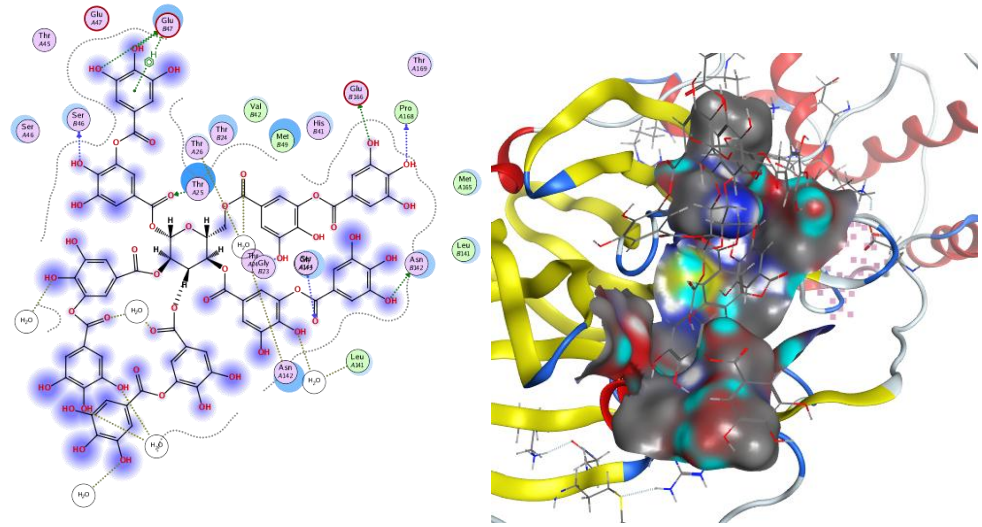

Figure 8. (5R81+Tannic acid).

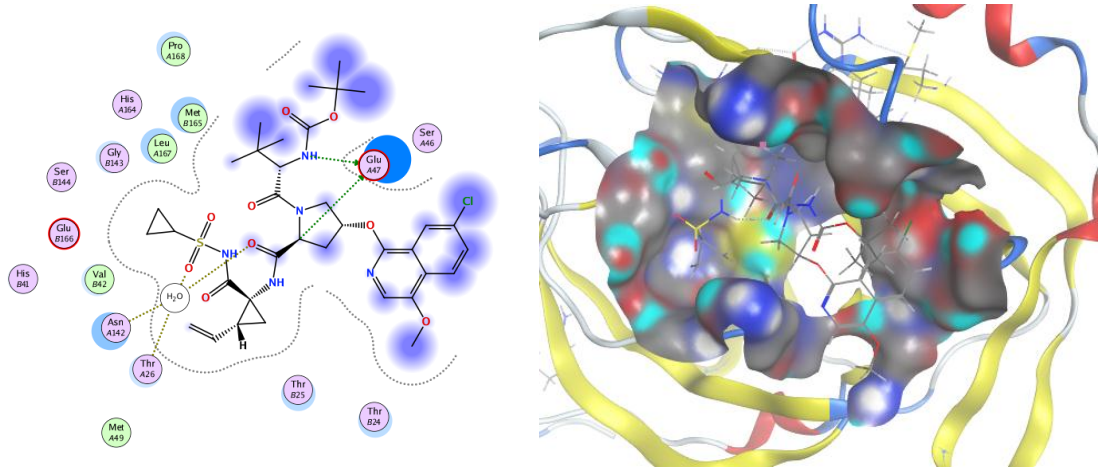

Figure 9. (5R81+ Asunaprevir).

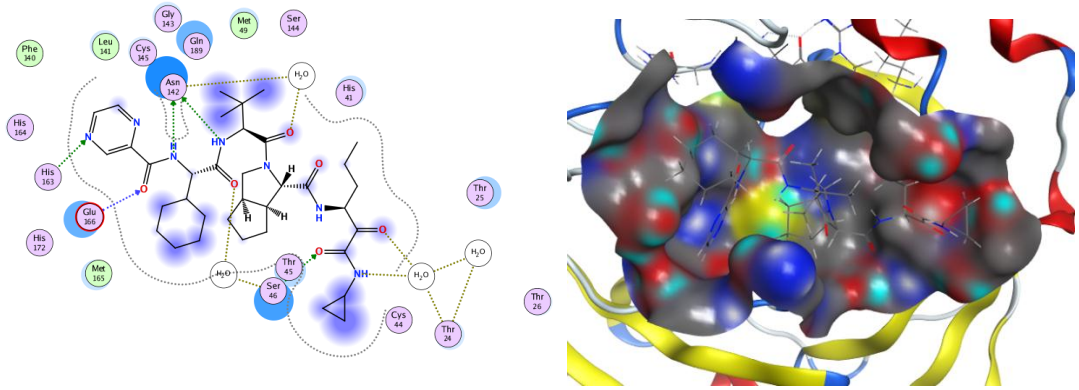

Figure 10. (5R82+ Telaprevir).

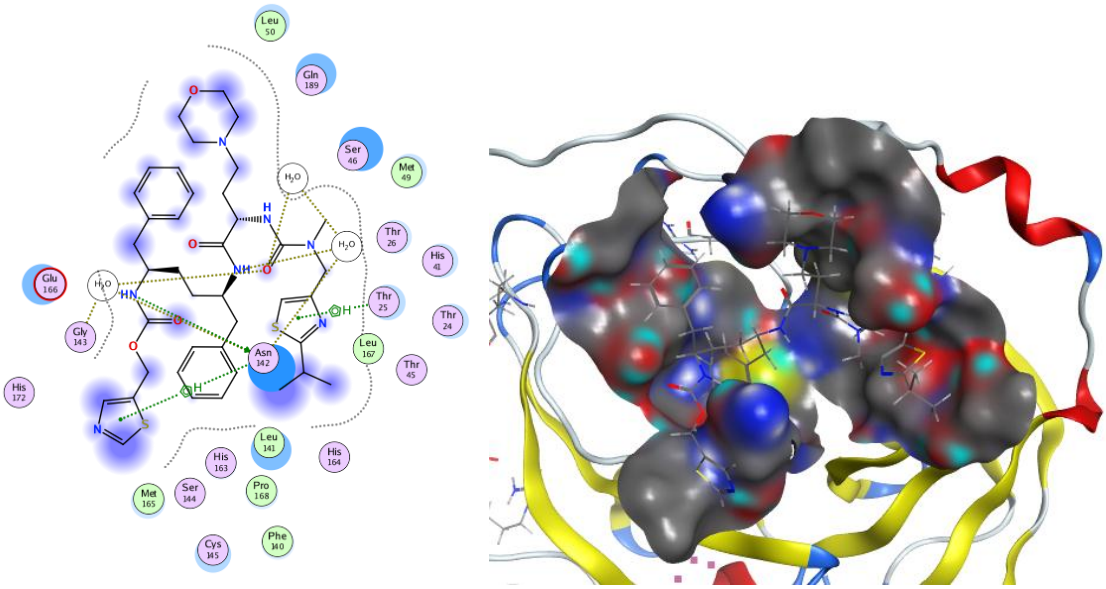

Figure 11. (5R82+Cobicistat).

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