Predicted antiviral drugs Darunavir, Indinavir and Rimantadine can potentially bind to neutralize COVID-19 conserved proteins

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Research

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Abstract

Background: Novel Coronavirus disease 2019 or COVID-19 has become a threat to human society due to fast spreading and increasing mortality. It uses vertebrate hosts and presently deploying humans. Life cycle and pathogenicity of COVID-19 have already been deciphered and possible drug target tests are on the way.

Results: The present study was aimed to analyze conserved Endoribonuclease, protease and replicase proteins of the virus as targets to all known drugs. A bioinformatics based web server Drug ReposeER predicted several drug binding motifs in these analyzed proteins. Results revealed that anti-viral Darunavir, Indinavir and Rimantadine were the most potent to have 3D-drug binding motifs on COVID-19 proteins.

Conclusions: Repurposing of the antiviral drugs Darunavir, Indinavir and Rimantadine to treat COVID-19 infected persons could be useful that can potentially prevent thousands of human mortality.

Background

COVID-19 has become a menace to the human kind that imposed epidemic condition. Great efforts are being carried out by the scientists to develop vaccine or a potent drug to curb human mortality. The virus has several types of vertebrate hosts including human and transmission occurs through direct contact or aerosols. It's a positive sense RNA virus with a genome of ~30 kb (1, 2). Like every animal virus their proteins hijack the cellular machineries to complete life cycle. These proteins are of great interest to the scientists to develop specific drug or vaccine against them. Search and trial for potential inhibitory drugs is on the way but they were proven ineffective to prevent patient death (3). The present work based on the fact that enzymes of any virus remain structurally and chemically conserved as they have to interact with human proteins and have to carry out same biochemical processes within cell. In the present study three structurally known enzymes of COVID-19, i.e., NSP15 endoribonuclease (PDB ID: 6VWW) (4), Main Protease (PDB ID: 6M03) (5), and NSP9 Replicase (PDB ID: 6W4B) (6) have been analyzed using Drug ReposeER web server program (<http://27.126.156.175/drreposed/>) (7) for their possible binding sites (8) to all drugs available in drug bank. Coronavirus endoribonuclease (NSP15/EndoU) is a hexameric protein that preferentially recognizes and cleaves RNA (1, 2, 9) and EndoU also evades host mediated viral double-stranded RNA recognition (10). Main protease (M^{Pro}) or NSP5 is essential for viral replication (1, 2, 11) whereas NSP9 replicase is dimeric and involved in viral RNA synthesis (1, 2, 12, 13).

Results And Discussion

DrReposER predicted numerous potential 3D-motifs of both left (L) and right (R) superpositions for 6VWW, 6M03, 6W4B (**Supplementary 1, Supplementary 2, Supplementary 3**). Known drugs that bind these motifs either bind human cellular, bacterial or viral proteins. From the hit results 16 anti-viral drugs were selected for their target specificities and effectiveness. The anti-viral drugs were presented in tabular formats (**Table 1 – 3**). Results showed that 21 unique potential 3D-motifs were predicted for (6VWW) Endoribonuclease (**Table 1**), 13 for (6M03) main Protease (**Table 2**) and 6 for (6W4B) Replicase (**Table 3**). The drugs were further analyzed and compared for their binding towards all the target proteins (**Table 4**). Results revealed that Darunavir (Ligand ID: 017), Indinavir (Ligand ID: MK1) and S-adenosylmethionine (SAM) have binding sites both on 6VWW and 6M03, whereas Ribavirin and Rimantadine (Ligand ID: RIM) have binding sites on 6M03 and 6W4B. Moreover, Tipranavir binding was predicted on all target proteins (**Table 4**). Other anti-viral drugs, i.e., Amprenavir, Atazanavir, Lopinavir, Saquinavir, Torimifene, Amphetamine, Nelfinavir, Nevirapine, Ritonavir and Grazoprevir had binding sites on any of the three analyzed proteins. From the results Darunavir, Indinavir and Rimantadine have been prioritized for their greater inhibitory binding to these proteins. Darunavir had 5 binding motifs (3LEU-23VAL-6VAL, 72ILE-157GLY-156VAL, 73LEU-80ILE-86ILE, 300LEU-212ILE-253ILE, and 300LEU-296ILE-253ILE) on 6VWW and 2 binding motifs (109GLY-200ILE-293PRO and 133ASN-195GLY-194ALA) on 6M03 (**Table1,2,4, Fig 1,2**). Indinavir had 3 binding motifs (122VAL-119PRO-80ILE, 173VAL-170GLY-169ILE and 321VAL-344PRO-323ILE) on 6VWW and a single motif (106ILE-109GLY-200ILE) on 6M03 (**Table1,2,4 Fig 1,2**) whereas Rimantadine had 3 predicted binding sites (255ALA-254SER-251GLY, 255ALA-254SER-258GLY and 285ALA-284SER-283GLY) on 6M03 and 3 binding sites (111VAL-108ALA-106SER, 111VAL-109ALA-106SER and 109ALA-106SER-105GLY) on 6W4B (**Table2,3,4, Fig 2,3**). Again minimum Root Mean Square Deviation (RMSD) for 6VWW-Darunavir and 6M03-Darunavir binding was 0.77 Å and 0.76 Å and known interaction for binding involves maximum of 22 and 26 residues respectively (**Table 1,2**). RMSD and residue binding of Indinavir to 6VWW and 6M03 were 0.87 Å & 0.82 Å, and 21 & 22 residues respectively (**Table 1,2**). Rimantadine accounts for 6M03 and 6W4B binding with RMSD of 0.88 Å & 0.90 Å and 9 & 10 residues respectively (**Table 2,3**).

From the resulted Table 4, it is evident that SAM, Tipranavir and Ribavirin showed predicted binding sites for the targets, however, Darunavir, Indinavir and Rimantadine binding outnumber them. Again some target sites coincide with Darunavir, Indinavir or Rimantadine as can be seen for Saquinavir. Hence, Darunavir, Indinavir and Rimantadine could be the choice of drugs to treat COVID-19. Along with these SAM may be administered which is not a classical anti-viral drug and have implications to treat Liver problems. Darunavir (DRV- Drugbank ID: DB01264) and Indinavir (IDV- Drugbank ID: DB00224) are members of Protease-inhibitor family of antiviral drugs to ward off HIV, on the other hand Rimantadine (RIM- Drugbank ID: DB00478) is an Influenza virus inhibitor (14). These drugs are potent to inhibit their designated targets and results of this analysis also provide data that these can effectively bind COVID-19 targeted proteins to inhibit disease outcome and prevent human death.

Conclusion

The findings strongly suggest that combination of antiviral drugs, Darunavir, Indinavir and Rimantadine can potentially inhibit COVID-19 enzymatic proteins. The targeted proteins are highly conserved and due to this reason inhibiting those can effectively inhibit the entire virus. Where no such drugs are proving ineffective to save thousands of lives, these predicted combinations of drugs must be clinically tested to cure patients. Practical implication of the findings can effectively save thousands of valuable lives. On the other hand vaccine development is on the way but the limitations of vaccine use is that it can not protect already infected patients showing disease outcomes and in those cases only effective drugs can save lives.

Methods

Key Resources Table

Resource	Source	Identifier
Deposited Data		
COVI-19 Endonuclease 3D-structure	Kim et al., 2020	PDB ID: 6VWW
COVI-19 Main Protease 3D-structure	Zhang et al., 2020	PDB ID: 6M03
COVI-19 Replicase 3D-structure	Tan et al., 2020	PDB ID: 6W4B
Web Server		
DrReposER	Ab Ghani et al., 2019	http://27.126.156.175/drreposed/

DrReposER has been used to find binding interfaces or 3D-motifs of target proteins (PDB ID: 6VWW, 6M03, 6W4B) for all possible drugs. The program uses SPRITE and ASSAM web servers to find amino acid side chains (8, 15, 16, 17). Drug ReposER compares structurally similar side chain arrangements from PDB repository and assign hit results for different drug targets in the query PDB ID.

Declarations

Ethics approval and consent to participate: Not applicable

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Tables

Table 1. Possible binding sites of NSP15 against known anti-viral drugs. Features of different drug binding motifs. HIV-1-Human Immunodeficiency virus 1, RMSD- Root Mean Square Deviation, Å-angstrom, ILE-isoleucine, GLY-glycine, VAL-valine, LEU-leucine, PRO-proline, ASP-aspartic acid

					(6VWW) ENDORIBONUCLEASE OF COVID-19	NSP15
DRUGS		TOTAL BINDING SITES				
AMPRENAVIR	KNOWN SIMILAR TARGET MOLECULE				PROTEASE, HIV-1	
	BINDING PROPERTIES	2	1	SUPERPOSITION TYPE	L	
				RMSD	0.90 Å	
				AMINO ACID TARGETS OF DRUG	72 ILE 157 GLY 156 VAL	
				NO. OF RESIDUES IN KNOWN BINDING	25	
				HUMAN SIMILAR TARGETS	4	
			2	SUPERPOSITION TYPE	L	
				RMSD	0.66 Å	
				AMINO ACID TARGETS OF DRUG	251 LEU 276 VAL 296 ILE	
				NO. OF RESIDUES IN KNOWN BINDING	19	
				HUMAN SIMILAR TARGETS	5	
ATAZANAVIR	KNOWN SIMILAR TARGET MOLECULE				PROTEASE, HIV-1	
	BINDING PROPERTIES	1	1	SUPERPOSITION TYPE	L	
				RMSD	0.83 Å	
				AMINO ACID TARGETS OF DRUG	72 ILE 157 GLY 156 VAL	
				NO. OF RESIDUES IN KNOWN BINDING	24	
				HUMAN SIMILAR TARGETS	4	
DARUNAVIR	KNOWN SIMILAR TARGET MOLECULE				PROTEASE, HIV-2	
	BINDING PROPERTIES	5	1	SUPERPOSITION TYPE	L	
				RMSD	1.00 Å	
				AMINO ACID TARGETS OF DRUG	3 LEU 23 VAL 6 VAL	
				NO. OF RESIDUES IN KNOWN BINDING	20	
				HUMAN SIMILAR TARGETS	6	
			2	SUPERPOSITION TYPE	L	
				RMSD	0.95 Å	
				AMINO ACID TARGETS OF DRUG	72 ILE 157 GLY 156 VAL	
				NO. OF RESIDUES IN KNOWN BINDING	20	
				HUMAN SIMILAR TARGETS	10	
			3	SUPERPOSITION TYPE	R	
				RMSD	0.77 Å	
				AMINO ACID TARGETS OF DRUG	73 LEU 80 ILE 86 ILE	
				NO. OF RESIDUES IN KNOWN BINDING	22	
				HUMAN SIMILAR TARGETS	12	
			4	SUPERPOSITION TYPE	R	
				RMSD	0.91 Å	
				AMINO ACID TARGETS	300 LEU	

			5	OF DRUG	212 ILE 253 ILE			
				NO. OF RESIDUES IN KNOWN BINDING	22			
				HUMAN SIMILAR TARGETS	12			
				SUPERPOSITION TYPE	L			
				RMSD	0.77 Å			
				AMINO ACID TARGETS OF DRUG	300 LEU 296 ILE 253 ILE			
				NO. OF RESIDUES IN KNOWN BINDING	22			
				HUMAN SIMILAR TARGETS	12			
INDINAVIR	KNOWN SIMILAR TARGET MOLECULE			PROTEASE RETROPEPSIN, HIV-1				
	BINDING PROPERTIES	3	1	SUPERPOSITION TYPE	R			
				RMSD	0.99 Å			
				AMINO ACID TARGETS OF DRUG	122 VAL 119 PRO 80 ILE			
				NO. OF RESIDUES IN KNOWN BINDING	21			
				HUMAN SIMILAR TARGETS	6			
			2	SUPERPOSITION TYPE	R			
				RMSD	0.87 Å			
				AMINO ACID TARGETS OF DRUG	173 VAL 170 GLY 169 ILE			
				NO. OF RESIDUES IN KNOWN BINDING	21			
				HUMAN SIMILAR TARGETS	3			
			3	SUPERPOSITION TYPE	L			
				RMSD	0.96 Å			
				AMINO ACID TARGETS OF DRUG	321 VAL 344 PRO 323 ILE			
				NO. OF RESIDUES IN KNOWN BINDING	21			
				HUMAN SIMILAR TARGETS	6			
			LOPINAVIR	KNOWN SIMILAR TARGET MOLECULE			PROTEASE, HIV-1	
				BINDING PROPERTIES	3	1	SUPERPOSITION TYPE	R
							RMSD	0.90 Å
							AMINO ACID TARGETS OF DRUG	122 VAL 119 PRO 80 ILE
							NO. OF RESIDUES IN KNOWN BINDING	23
							HUMAN SIMILAR TARGETS	6
2	SUPERPOSITION TYPE	R						
	RMSD	0.80 Å						
	AMINO ACID TARGETS OF DRUG	247 GLY 248 GLY 236 ILE						
	NO. OF RESIDUES IN KNOWN BINDING	27						
	HUMAN SIMILAR TARGETS	6						
3	SUPERPOSITION TYPE	L						
	RMSD	0.89 Å						
	AMINO ACID TARGETS OF DRUG	321 VAL 344 PRO 323 ILE						
	NO. OF RESIDUES IN	23						

				KNOWN BINDING	
				HUMAN SIMILAR TARGETS	6
SAM (S-adenosylmethionine)	KNOWN SIMILAR TARGET MOLECULE				RNA directed RNA polymerase, Human metapneumovirus
	BINDING PROPERTIES	2	1	SUPERPOSITION TYPE	R
				RMSD	0.83 Å
				AMINO ACID TARGETS OF DRUG	162 VAL 79 ASP 88 ASP
				NO. OF RESIDUES IN KNOWN BINDING	15
				HUMAN SIMILAR TARGETS	10
			2	SUPERPOSITION TYPE	R
				RMSD	0.73 Å
				AMINO ACID TARGETS OF DRUG	162 VAL 79 ASP 273 ASP
				NO. OF RESIDUES IN KNOWN BINDING	15
				HUMAN SIMILAR TARGETS	10
SAQUINAVIR	KNOWN SIMILAR TARGET MOLECULE				PROTEASE, HIV-1
	BINDING PROPERTIES	3	1	SUPERPOSITION TYPE	L
				RMSD	0.81 Å
				AMINO ACID TARGETS OF DRUG	72 ILE 157 GLY 156 VAL
				NO. OF RESIDUES IN KNOWN BINDING	31
				HUMAN SIMILAR TARGETS	11
			2	SUPERPOSITION TYPE	R
				RMSD	0.92 Å
				AMINO ACID TARGETS OF DRUG	122 VAL 119 PRO 80 ILE
				NO. OF RESIDUES IN KNOWN BINDING	31
				HUMAN SIMILAR TARGETS	5
			3	SUPERPOSITION TYPE	L
				RMSD	0.68 Å
				AMINO ACID TARGETS OF DRUG	321 VAL 344 PRO 323 ILE
				NO. OF RESIDUES IN KNOWN BINDING	22
				HUMAN SIMILAR TARGETS	9
TIPRANAVIR	KNOWN SIMILAR TARGET MOLECULE				PROTEASE, HIV-1
	BINDING PROPERTIES	1	1	SUPERPOSITION TYPE	L
				RMSD	0.88 Å
				AMINO ACID TARGETS OF DRUG	72 ILE 157 GLY 156 VAL
				NO. OF RESIDUES IN KNOWN BINDING	27
				HUMAN SIMILAR TARGETS	3
TORIMIFENE	KNOWN SIMILAR TARGET MOLECULE				ENV, GLYCOPROTEIN-1, ZAIRE EBOLA VIRUS
	BINDING PROPERTIES	1	1	SUPERPOSITION TYPE	L
				RMSD	0.88 Å
				AMINO ACID TARGETS OF DRUG	72 ILE 157 GLY 156 VAL

				NO. OF RESIDUES IN KNOWN BINDING	27
				HUMAN SIMILAR TARGETS	3

Table 2. Possible binding sites of Protease against known anti-viral drugs. Features of different drug binding motifs. HIV-1-Human Immunodeficiency virus 1, RMSD- Root Mean Square Deviation, Å-angstrom, ILE-isoleucine, GLY-glycine, VAL-valine, LEU-leucine, PRO-proline, ASP-aspartic acid, ASN-asparagine, ALA-alanine, THR-threonine, LYS-lysine, SER-serine.

					(6M03) MAIN PROTEASE OF COVID-19
DRUGS		TOTAL BINDING SITES			
AMPHETAMINE	KNOWN SIMILAR TARGET MOLECULE				Polymerase Polyprotein, HIV-1
	BINDING PROPERTIES	1	1	SUPERPOSITION TYPE	L
				RMSD	0.93 Å
				AMINO ACID TARGETS OF DRUG	122 PRO 120 GLY 28 ASN
				NO. OF RESIDUES IN KNOWN BINDING	16
				HUMAN SIMILAR TARGETS	0
DARUNAVIR	KNOWN SIMILAR TARGET MOLECULE				HIV-1 PROTEASE
	BINDING PROPERTIES	2	1	SUPERPOSITION TYPE	L
				RMSD	1.06 Å
				AMINO ACID TARGETS OF DRUG	109 GLY 200 ILE 293 PRO
				NO. OF RESIDUES IN KNOWN BINDING	26
				HUMAN SIMILAR TARGETS	0
			2	SUPERPOSITION TYPE	R
				RMSD	0.76 Å
				AMINO ACID TARGETS OF DRUG	133 ASN 195 GLY 194 ALA
				NO. OF RESIDUES IN KNOWN BINDING	26
				HUMAN SIMILAR TARGETS	2
INDINAVIR	KNOWN SIMILAR TARGET MOLECULE				PROTEASE RETROPEPSIN, HIV-1
	BINDING PROPERTIES	1	1	SUPERPOSITION TYPE	L
				RMSD	0.81 Å
				AMINO ACID TARGETS OF DRUG	106 ILE 109 GLY 200 ILE
				NO. OF RESIDUES IN KNOWN BINDING	22
				HUMAN SIMILAR TARGETS	4
NELFINAVIR	KNOWN SIMILAR TARGET MOLECULE				PROTEASE RETROPEPSIN, HIV-1
	BINDING PROPERTIES	1	1	SUPERPOSITION TYPE	L
				RMSD	1.05 Å
				AMINO ACID TARGETS OF DRUG	153 ASP 292 THR 293 PRO
				NO. OF RESIDUES IN KNOWN BINDING	30
				HUMAN SIMILAR TARGETS	13
NEVIRAPINE	KNOWN SIMILAR TARGET MOLECULE				REVERSE TRANSCRIPTASE, HIV-1
	BINDING PROPERTIES	1	1	SUPERPOSITION TYPE	R
				RMSD	1.10 Å
				AMINO ACID TARGETS OF DRUG	88 LYS 86 VAL 30 LEU

				NO. OF RESIDUES IN KNOWN BINDING	7
				HUMAN SIMILAR TARGETS	13
RIBAVIRIN	KNOWN SIMILAR TARGET MOLECULE				RNA POLYMERASE, NORWALK VIRUS
	BINDING PROPERTIES	1	1	SUPERPOSITION TYPE	L
				RMSD	1.06 Å
				AMINO ACID TARGETS OF DRUG	198 THR 199 THR 238 ASN
				NO. OF RESIDUES IN KNOWN BINDING	9
				HUMAN SIMILAR TARGETS	2
RIMANTADINE	KNOWN SIMILAR TARGET MOLECULE				M2 PROTEIN, INFLUENZA A
	BINDING PROPERTIES	3	1	SUPERPOSITION TYPE	R
				RMSD	0.95 Å
				AMINO ACID TARGETS OF DRUG	255 ALA 254 SER 251 GLY
				NO. OF RESIDUES IN KNOWN BINDING	9
				HUMAN SIMILAR TARGETS	0
			2	SUPERPOSITION TYPE	L
				RMSD	0.88 Å
				AMINO ACID TARGETS OF DRUG	255 ALA 254 SER 258 GLY
				NO. OF RESIDUES IN KNOWN BINDING	9
				HUMAN SIMILAR TARGETS	0
			3	SUPERPOSITION TYPE	L
				RMSD	1.00 Å
				AMINO ACID TARGETS OF DRUG	285 ALA 284 SER 283 GLY
				NO. OF RESIDUES IN KNOWN BINDING	9
				HUMAN SIMILAR TARGETS	0
RITONAVIR	KNOWN SIMILAR TARGET MOLECULE				POLYMERASE POLYPROTEIN, HIV-1
	BINDING PROPERTIES	1	1	SUPERPOSITION TYPE	L
				RMSD	0.82 Å
				AMINO ACID TARGETS OF DRUG	106 ILE 109 GLY 200 ILE
				NO. OF RESIDUES IN KNOWN BINDING	18
				HUMAN SIMILAR TARGETS	4
SAM (S-adenosylmethionine)	KNOWN SIMILAR TARGET MOLECULE				NSP5, MODOC VIRUS
	BINDING PROPERTIES	1	1	SUPERPOSITION TYPE	L
				RMSD	0.87 Å
				AMINO ACID TARGETS OF DRUG	92 ASP 91 VAL 93 THR
				NO. OF RESIDUES IN KNOWN BINDING	14
				HUMAN SIMILAR TARGETS	10
TIPRANAVIR	KNOWN SIMILAR TARGET MOLECULE				PROTEASE,

BINDING PROPERTIES	1	1	SUPERPOSITION TYPE	HIV-1
			RMSD	L
			AMINO ACID TARGETS OF DRUG	1.17 Å
			NO. OF RESIDUES IN KNOWN BINDING	94 ALA 34 ASP 33 ASP
			HUMAN SIMILAR TARGETS	27
			3	

Table 3. Possible binding sites of NSP9 against known anti-viral drugs. Features of different drug binding motifs. HIV-1-Human Immunodeficiency virus 1, RMSD- Root Mean Square Deviation, Å-angstrom, ILE-isoleucine, GLY-glycine, VAL-valine, ASP-aspartic acid, ASN-asparagine, ALA-alanine, THR-threonine, LYS-lysine, SER-serine.

					(6W4B) NSP9 Replicase of COVID-19
DRUGS		TOTAL BINDING SITES			
GRAZOPREVR	KNOWN SIMILAR TARGET MOLECULE				NS3 PROTEASE, NS4A PROTEIN, Hepacivirus C
	BINDING PROPERTIES	1	1	SUPERPOSITION TYPE	L
				RMSD	0.94 Å
				AMINO ACID TARGETS OF DRUG	66 ILE 59 LYS 62 GLY
				NO. OF RESIDUES IN KNOWN BINDING	16
				HUMAN SIMILAR TARGETS	8
RIBAVIRIN	KNOWN SIMILAR TARGET MOLECULE				RNA POLYMERASE, NORWALK VIRUS
	BINDING PROPERTIES	1	1	SUPERPOSITION TYPE	R
				RMSD	0.80 Å
				AMINO ACID TARGETS OF DRUG	36 THR 35 THR 34 ASN
				NO. OF RESIDUES IN KNOWN BINDING	09
				HUMAN SIMILAR TARGETS	2
RIMANTADINE	KNOWN SIMILAR TARGET MOLECULE				M2, BM2 PROTEIN, INFLUENZA A,B
	BINDING PROPERTIES	3	1	SUPERPOSITION TYPE	L
				RMSD	0.90 Å
				AMINO ACID TARGETS OF DRUG	109 ALA 106 SER 105 GLY
				NO. OF RESIDUES IN KNOWN BINDING	9
			HUMAN SIMILAR TARGETS	0	
2	SUPERPOSITION	R			

				TYPE	
				RMSD	1.10 Å
				AMINO ACID TARGETS OF DRUG	111 VAL 108 VAL 106 SER
				NO. OF RESIDUES IN KNOWN BINDING	10
				HUMAN SIMILAR TARGETS	0
			3	SUPERPOSITION TYPE	R
				RMSD	1.26 Å
				AMINO ACID TARGETS OF DRUG	111 VAL 109 ALA 106 SER
				NO. OF RESIDUES IN KNOWN BINDING	10
				HUMAN SIMILAR TARGETS	0
TIPRANAVIR	KNOWN SIMILAR TARGET MOLECULE				PROTEASE, HIV-1
	BINDING PROPERTIES	1	1	SUPERPOSITION TYPE	L
				RMSD	1.21 Å
				AMINO ACID TARGETS OF DRUG	16 ALA 26 ASP 27 ASP
				NO. OF RESIDUES IN KNOWN BINDING	27
				HUMAN SIMILAR TARGETS	3

Table 4. Comparison of binding sites of all selected drugs. Out of 16 anti-viral drugs 3 have been selected for their greater binding.

DRUGS	6VWW	6M03	6W4B
Amphetamine	-	+	-
Amprenavir	++	-	-
Atazanavir	+	-	-
Darunavir	+++++	++	-
Grazoprevir	-	-	+
Indinavir	+++	+	-
Lopinavir	+++	-	-
Nelfinavir	-	+	-
Nevirapine	-	+	-
Ribavirin	-	+	+
Rimantadine	-	+++	+++
Ritonavir	-	+	-
S-adenosylmethionine	++	+	-
Saquinavir	+++	-	-
Tipranavir	+	+	+
Torimifene	+	-	-

Figures

Figure 1

3D-binding interfaces of NSP15 Endoribonuclease with Darunavir & Indinavir. a. Chemical structure of Darunavir. b-f. Binding pockets of Darunavir with different interacting motifs. g. All the binding pockets of NSP15 with Darunavir. h. Chemical structure of Indinavir. i-k. Binding pockets of Indinavir with different interacting motifs. l. All the binding pockets of NSP15 with Indinavir. m. Combined binding interfaces of Darunavir and Indinavir with NSP15. DRV-Darunavir, IDV-Indinavir.

Figure 2

3D-binding interfaces of Main Protease with Rimantadine, Darunavir & Indinavir. a. Chemical structure of Rimantadine. b-d. Binding pockets of Rimantadine with different interacting motifs. e. All the binding pockets of Protease with Rimantadine. f. Chemical structure of Darunavir. g, h. Binding pockets of Darunavir with different interacting motifs. i. All the binding pockets of Protease with Darunavir. j. Chemical structure of Indinavir. k. Binding pockets of Indinavir with different interacting motifs. l. Combined binding interfaces of Rimantadine, Darunavir and Indinavir with Main Protease. RIM-Rimantadine, DRV-Darunavir, IDV-Indinavir.

Figure 3

3D-binding interfaces of NSP9 Replicase with Rimantadine. a. Chemical structure of Rimantadine. b-d. Binding pockets of Rimantadine with different interacting motifs. e. All the binding pockets of Replicase with Rimantadine. RIM-Rimantadine.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [S1LISTOFHITSFOR6VWW.docx](#)
- [S2LISTOFHITSOF6M03MAINPROTEASE.docx](#)
- [S3LISTOFHITSFOR6W4B.docx](#)