Chemical system biology approach to identify multi-targeting FDA inhibitors for treating COVID-19 and associated health complications

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Running Title- Multi-targeting FDA inhibitors for COVID-19

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Supplementary Table-1 Active site retrieved from published literatures

SL. No	Proteins	Accession No.	PDB ID	ACTIVE SITE	References
1	**3C-like proteinase**	YP_0097 25301.1	6LU7 bounded with N3	C145, S46, Y54	[1]
2	**RNA-dependent RNA polymerase**	YP_0097 25307.1	6M71	Arg553, Arg555, Lys621, Asp623 and Ser814	[2, 3]
3	**helicase**	YP_0097 25308.1	Not available	K288, S289, D374, E375, Q404, and R567	[4, 5]
4	**3'-to-5' exonuclease**	YP_0097 25309.1	Not available	Asp90, Glu92, Glu191 HIs268, Asp 273 for SARS	[6]
5	**endoRNAse**	YP_0097 25310.1	6VWW	His235, His250, Lys290, Thr341, Tyr343, and Ser294	[7, 8]
6	**2'-O-ribose methyltransferase**	YP_0097 25311.1	6W61	Lys46, Asp130, Lys170, and Glu203	[9]
7	**Spike glycoprotein**	YP_0097 24390.1	6VXX	TYR 449, THR 500, GLN 493, GLN 498, TYR 501, GLY 502 and TYR 505 for COVID-19	[10]
8	**Spike glycoprotein / HUMAN_ACE2 hetero-oligomeric complex**	YP_0097 24390.1	6LZG	A475, N487, E484 and Y453 of spike glycoprotein interacting with hACE2 S19, Q24, K31, and H34 respectively	[11]
9	**Papain-like proteinase (PL-PRO)**	YP_0097 25299.1	6W9C	Cys112, His272 and Asp286	[12]
10	**Nucleocapsid**	YP_0097 24393.1	6M3M	T55, A56, N48, N49, T50, A51 and R89	[13]

Supplementary Table-2 List of protein-ligand interaction between RNA dependent RNA polymerase and Rutin hydrate

PDB code: **6M71** Ligand: **Rutin hydrate (RUT)**

Hydrogen bonds

	<----- A T O M 1 ----->					<----- A T O M 2 ----->					
	Atom no.	Atom name	Res name	Res no.	Chain		Atom no.	Atom name	Res name	Res no.	Chain	Distance
1.	8314	OG	SER	549	A	<--	18049	O6	RUT	900		3.12
2.	8373	NE	ARG	553	A	-->	18037	O3	RUT	900		3.29
3.	8375	NH1	ARG	553	A	-->	18062	O13	RUT	900		2.97
4.	8376	NH2	ARG	553	A	-->	18062	O13	RUT	900		2.74
5.	8424	N	THR	556	A	-->	18069	O16	RUT	900		2.96
6.	8427	O	THR	556	A	<--	18064	O14	RUT	900		3.08
7.	8427	O	THR	556	A	<--	18067	O15	RUT	900		2.76
8.	9396	N	TYR	619	A	-->	18053	O8	RUT	900		3.10
9.	9399	O	TYR	619	A	<--	18052	O7	RUT	900		3.35
10.	9453	N	CYS	622	A	-->	18057	O10	RUT	900		2.82
11.	9470	OD1	ASP	623	A	<--	18057	O10	RUT	900		2.86
12.	10373	OG	SER	682	A	-->	18067	O15	RUT	900		2.94
13.	11607	O	ASP	760	A	<--	18053	O8	RUT	900		2.86
14.	11610	OD1	ASP	760	A	<--	18053	O8	RUT	900		3.27

Non-bonded contacts

	<----- A T O M 1 ----->					<----- A T O M 2 ----->					
	Atom no.	Atom name	Res name	Res no.	Chain		Atom no.	Atom name	Res name	Res no.	Chain	Distance
1.	8314	OG	SER	549	A	---	18049	O6	RUT	900		3.12
2.	8337	CE	LYS	551	A	---	18049	O6	RUT	900		3.71
3.	8338	NZ	LYS	551	A	---	18042	C13	RUT	900		3.56
4.	8338	NZ	LYS	551	A	---	18049	O6	RUT	900		3.33
5.	8373	NE	ARG	553	A	---	18037	O3	RUT	900		3.29
6.	8374	CZ	ARG	553	A	---	18037	O3	RUT	900		3.89
7.	8374	CZ	ARG	553	A	---	18062	O13	RUT	900		3.28
8.	8374	CZ	ARG	553	A	---	18068	C27	RUT	900		3.81
9.	8375	NH1	ARG	553	A	---	18062	O13	RUT	900		2.97
10.	8375	NH1	ARG	553	A	---	18065	C25	RUT	900		3.46
11.	8375	NH1	ARG	553	A	---	18068	C27	RUT	900		2.85
12.	8376	NH2	ARG	553	A	---	18037	O3	RUT	900		3.63
13.	8376	NH2	ARG	553	A	---	18043	O4	RUT	900		3.72
14.	8376	NH2	ARG	553	A	---	18055	C20	RUT	900		3.72
15.	8376	NH2	ARG	553	A	---	18058	O11	RUT	900		3.87
16.	8376	NH2	ARG	553	A	---	18060	C22	RUT	900		3.29
17.	8376	NH2	ARG	553	A	---	18062	O13	RUT	900		2.74
18.	8424	N	THR	556	A	---	18069	O16	RUT	900		2.96
19.	8425	CA	THR	556	A	---	18069	O16	RUT	900		3.54
20.	8426	C	THR	556	A	---	18067	O15	RUT	900		3.87
21.	8426	C	THR	556	A	---	18069	O16	RUT	900		3.64
22.	8427	O	THR	556	A	---	18061	C23	RUT	900		3.83
23.	8427	O	THR	556	A	---	18063	C24	RUT	900		3.54
24.	8427	O	THR	556	A	---	18064	O14	RUT	900		3.08
25.	8427	O	THR	556	A	---	18066	C26	RUT	900		3.76
26.	8427	O	THR	556	A	---	18067	O15	RUT	900		2.76

27.	8427	O	THR	556	A	---	18069	O16	RUT	900	3.02
28.	8428	CB	THR	556	A	---	18069	O16	RUT	900	3.75
29.	8429	OG1	THR	556	A	---	18066	C26	RUT	900	3.84
30.	8429	OG1	THR	556	A	---	18069	O16	RUT	900	2.84
31.	9385	CA	ASP	618	A	---	18053	O8	RUT	900	3.84
32.	9388	CB	ASP	618	A	---	18040	C11	RUT	900	3.74
33.	9396	N	TYR	619	A	---	18040	C11	RUT	900	3.73
34.	9396	N	TYR	619	A	---	18045	C15	RUT	900	3.88
35.	9396	N	TYR	619	A	---	18053	O8	RUT	900	3.10
36.	9399	O	TYR	619	A	---	18040	C11	RUT	900	3.65
37.	9399	O	TYR	619	A	---	18052	O7	RUT	900	3.35
38.	9400	CB	TYR	619	A	---	18053	O8	RUT	900	3.89
39.	9431	N	LYS	621	A	---	18052	O7	RUT	900	3.48
40.	9431	N	LYS	621	A	---	18057	O10	RUT	900	3.60
41.	9432	CA	LYS	621	A	---	18057	O10	RUT	900	3.30
42.	9433	C	LYS	621	A	---	18057	O10	RUT	900	3.28
43.	9453	N	CYS	622	A	---	18051	C19	RUT	900	3.87
44.	9453	N	CYS	622	A	---	18057	O10	RUT	900	2.82
45.	9454	CA	CYS	622	A	---	18057	O10	RUT	900	3.75
46.	9457	CB	CYS	622	A	---	18057	O10	RUT	900	3.87
47.	9464	N	ASP	623	A	---	18057	O10	RUT	900	3.60
48.	9469	CG	ASP	623	A	---	18056	C21	RUT	900	3.66
49.	9469	CG	ASP	623	A	---	18057	O10	RUT	900	3.75
50.	9469	CG	ASP	623	A	---	18059	O12	RUT	900	3.47
51.	9470	OD1	ASP	623	A	---	18051	C19	RUT	900	3.73
52.	9470	OD1	ASP	623	A	---	18056	C21	RUT	900	3.42
53.	9470	OD1	ASP	623	A	---	18057	O10	RUT	900	2.86
54.	9470	OD1	ASP	623	A	---	18059	O12	RUT	900	3.10
55.	9471	OD2	ASP	623	A	---	18056	C21	RUT	900	3.83
56.	9471	OD2	ASP	623	A	---	18058	O11	RUT	900	3.76
57.	9471	OD2	ASP	623	A	---	18059	O12	RUT	900	3.42
58.	9471	OD2	ASP	623	A	---	18063	C24	RUT	900	3.31
59.	9471	OD2	ASP	623	A	---	18065	C25	RUT	900	3.11
60.	9471	OD2	ASP	623	A	---	18066	C26	RUT	900	3.19
61.	9471	OD2	ASP	623	A	---	18068	C27	RUT	900	3.84
62.	9485	NH1	ARG	624	A	---	18066	C26	RUT	900	3.77
63.	9485	NH1	ARG	624	A	---	18068	C27	RUT	900	3.75
64.	10372	CB	SER	682	A	---	18067	O15	RUT	900	3.12
65.	10373	OG	SER	682	A	---	18067	O15	RUT	900	2.94
66.	11607	O	ASP	760	A	---	18046	O5	RUT	900	3.48
67.	11607	O	ASP	760	A	---	18053	O8	RUT	900	2.86
68.	11609	CG	ASP	760	A	---	18046	O5	RUT	900	3.52
69.	11609	CG	ASP	760	A	---	18053	O8	RUT	900	3.76
70.	11610	OD1	ASP	760	A	---	18039	C10	RUT	900	3.79
71.	11610	OD1	ASP	760	A	---	18045	C15	RUT	900	3.65
72.	11610	OD1	ASP	760	A	---	18046	O5	RUT	900	3.55
73.	11610	OD1	ASP	760	A	---	18053	O8	RUT	900	3.27
74.	11611	OD2	ASP	760	A	---	18046	O5	RUT	900	3.23
Number of hydrogen bonds: 14											
Number of non-bonded contacts: 74											

Supplementary Table-3 List of protein-ligand interaction between exonuclease and Silymarin

PDB code: No PDB (**Exonuclease**) Ligand: **Silymarin (SYL)**

Hydrogen bonds

<----- A T O M 1 -----> <----- A T O M 2 ----->

	Atom no.	Atom name	Res name	Res no.	Chain		Atom no.	Atom name	Res name	Res no.	Chain	Distance
1.	1417	O	VAL	91	A	<--	8275	O7	SYL	900		2.78
2.	2984	OE2	GLU	191	A	<--	8275	O7	SYL	900		3.01
3.	4237	OD1	ASP	273	A	<--	8260	O3	SYL	900		3.26

Non-bonded contacts

<----- A T O M 1 -----> <----- A T O M 2 ----->

	Atom no.	Atom name	Res name	Res no.	Chain		Atom no.	Atom name	Res name	Res no.	Chain	Distance
1.	1406	CG	ASP	90	A	---	8275	O7	SYL	900		3.79
2.	1407	OD1	ASP	90	A	---	8275	O7	SYL	900		3.38
3.	1408	OD2	ASP	90	A	---	8274	C25	SYL	900		3.88
4.	1408	OD2	ASP	90	A	---	8275	O7	SYL	900		3.75
5.	1416	C	VAL	91	A	---	8274	C25	SYL	900		3.62
6.	1416	C	VAL	91	A	---	8275	O7	SYL	900		3.73
7.	1417	O	VAL	91	A	---	8274	C25	SYL	900		2.82
8.	1417	O	VAL	91	A	---	8275	O7	SYL	900		2.78
9.	1431	CA	GLU	92	A	---	8274	C25	SYL	900		3.79
10.	1445	N	GLY	93	A	---	8247	C4	SYL	900		3.63
11.	1445	N	GLY	93	A	---	8248	C5	SYL	900		3.27
12.	1445	N	GLY	93	A	---	8249	C6	SYL	900		3.68
13.	1446	CA	GLY	93	A	---	8248	C5	SYL	900		3.74
14.	1446	CA	GLY	93	A	---	8249	C6	SYL	900		3.84
15.	1446	CA	GLY	93	A	---	8271	O5	SYL	900		3.72
16.	1447	C	GLY	93	A	---	8248	C5	SYL	900		3.63
17.	1447	C	GLY	93	A	---	8271	O5	SYL	900		3.53
18.	1448	O	GLY	93	A	---	8248	C5	SYL	900		3.19
19.	1448	O	GLY	93	A	---	8249	C6	SYL	900		3.86
20.	1448	O	GLY	93	A	---	8271	O5	SYL	900		3.73
21.	1452	N	CYS	94	A	---	8271	O5	SYL	900		3.88
22.	1595	CG	ASN	104	A	---	8271	O5	SYL	900		3.39
23.	1597	OD1	ASN	104	A	---	8271	O5	SYL	900		3.20
24.	1596	ND2	ASN	104	A	---	8271	O5	SYL	900		3.70
25.	1596	ND2	ASN	104	A	---	8272	O6	SYL	900		3.46
26.	2141	CG	PRO	141	A	---	8248	C5	SYL	900		3.23
27.	2141	CG	PRO	141	A	---	8249	C6	SYL	900		3.83
28.	2141	CG	PRO	141	A	---	8271	O5	SYL	900		3.87
29.	2207	CE1	PHE	146	A	---	8247	C4	SYL	900		3.87
30.	2207	CE1	PHE	146	A	---	8255	O2	SYL	900		3.68
31.	2904	CD1	TRP	186	A	---	8276	O8	SYL	900		3.84
32.	2984	OE2	GLU	191	A	---	8275	O7	SYL	900		3.01
33.	3933	CB	ASN	252	A	---	8267	C20	SYL	900		3.53
34.	3933	CB	ASN	252	A	---	8268	C21	SYL	900		3.57
35.	3933	CB	ASN	252	A	---	8277	O9	SYL	900		3.75

36.	3935	ND2	ASN	252	A	---	8268	C21	SYL	900		3.82
37.	3935	ND2	ASN	252	A	---	8269	C22	SYL	900		3.41
38.	3935	ND2	ASN	252	A	---	8270	C23	SYL	900		3.63
39.	3935	ND2	ASN	252	A	---	8278	O10	SYL	900		3.61
40.	3947	CB	LEU	253	A	---	8260	O3	SYL	900		3.70
41.	3947	CB	LEU	253	A	---	8263	C17	SYL	900		3.86
42.	3947	CB	LEU	253	A	---	8276	O8	SYL	900		3.28
43.	3950	CD2	LEU	253	A	---	8260	O3	SYL	900		3.83
44.	3962	N	GLN	254	A	---	8260	O3	SYL	900		3.65
45.	4236	CG	ASP	273	A	---	8256	C11	SYL	900		3.82
46.	4236	CG	ASP	273	A	---	8261	C15	SYL	900		3.74
47.	4237	OD1	ASP	273	A	---	8260	O3	SYL	900		3.26
48.	4237	OD1	ASP	273	A	---	8261	C15	SYL	900		3.31
49.	4237	OD1	ASP	273	A	---	8262	C16	SYL	900		3.75
50.	4238	OD2	ASP	273	A	---	8252	O1	SYL	900		3.79
51.	4238	OD2	ASP	273	A	---	8253	C9	SYL	900		3.73
52.	4238	OD2	ASP	273	A	---	8256	C11	SYL	900		2.97
53.	4238	OD2	ASP	273	A	---	8257	C12	SYL	900		3.74
54.	4238	OD2	ASP	273	A	---	8261	C15	SYL	900		3.85
Number of hydrogen bonds: 3												
Number of non-bonded contacts: 54												

Supplementary Table-4 List of protein-ligand interaction between Helicase and Luteolin

PDB code: No PDB (Helicase) Ligand: Luteolin (LUT)												
Non-bonded contacts												

	<----- A T O M 1 ----->						<----- A T O M 2 ----->					
	Atom no.	Atom name	Res name	Res no.	Chain		Atom no.	Atom name	Res name	Res no.	Chain	Distance
1.	4407	NZ	LYS	288	A	---	9312	C13	LUT	900		3.45
2.	4407	NZ	LYS	288	A	---	9313	C14	LUT	900		3.06
3.	4407	NZ	LYS	288	A	---	9314	C15	LUT	900		3.52
4.	4407	NZ	LYS	288	A	---	9315	O5	LUT	900		3.03
5.	4407	NZ	LYS	288	A	---	9316	O6	LUT	900		3.80
6.	4421	N	SER	289	A	---	9316	O6	LUT	900		3.83
7.	4425	CB	SER	289	A	---	9315	O5	LUT	900		3.37
8.	4425	CB	SER	289	A	---	9316	O6	LUT	900		3.35
9.	4426	OG	SER	289	A	---	9315	O5	LUT	900		3.28
10.	4784	CA	ALA	313	A	---	9310	C11	LUT	900		3.66
11.	4787	CB	ALA	313	A	---	9310	C11	LUT	900		3.70
12.	4825	CB	ALA	316	A	---	9303	C8	LUT	900		3.34
13.	4825	CB	ALA	316	A	---	9304	C9	LUT	900		3.70
14.	4825	CB	ALA	316	A	---	9309	C10	LUT	900		3.70
15.	4825	CB	ALA	316	A	---	9314	C15	LUT	900		3.63
16.	5762	CG	ASP	374	A	---	9311	C12	LUT	900		3.90
17.	5762	CG	ASP	374	A	---	9316	O6	LUT	900		3.30

18.	5763	OD1	ASP	374	A	---	9316	O6	LUT	900	3.36
19.	5764	OD2	ASP	374	A	---	9311	C12	LUT	900	3.72
20.	5764	OD2	ASP	374	A	---	9312	C13	LUT	900	3.52
21.	5764	OD2	ASP	374	A	---	9316	O6	LUT	900	2.66
22.	5774	CG	GLU	375	A	---	9311	C12	LUT	900	3.82
23.	5775	CD	GLU	375	A	---	9310	C11	LUT	900	3.69
24.	5777	OE2	GLU	375	A	---	9301	C6	LUT	900	3.78
25.	5777	OE2	GLU	375	A	---	9305	O1	LUT	900	3.23
26.	5777	OE2	GLU	375	A	---	9310	C11	LUT	900	3.16
27.	5777	OE2	GLU	375	A	---	9311	C12	LUT	900	3.86
28.	8299	O	ASP	534	A	---	9306	O2	LUT	900	3.70
29.	8333	O	GLN	537	A	---	9296	C1	LUT	900	3.85
30.	8333	O	GLN	537	A	---	9297	C2	LUT	900	3.89
31.	8333	O	GLN	537	A	---	9298	C3	LUT	900	3.66
32.	8333	O	GLN	537	A	---	9299	C4	LUT	900	3.37
33.	8333	O	GLN	537	A	---	9300	C5	LUT	900	3.34
34.	8333	O	GLN	537	A	---	9301	C6	LUT	900	3.58
35.	8333	O	GLN	537	A	---	9305	O1	LUT	900	3.88
36.	8336	CD	GLN	537	A	---	9301	C6	LUT	900	3.75
37.	8336	CD	GLN	537	A	---	9306	O2	LUT	900	3.74
38.	8338	OE1	GLN	537	A	---	9296	C1	LUT	900	3.31
39.	8338	OE1	GLN	537	A	---	9301	C6	LUT	900	3.33
40.	8338	OE1	GLN	537	A	---	9306	O2	LUT	900	2.69
Number of non-bonded contacts: 40											

Supplementary Table-5 List of protein-ligand interaction between Methyl transferase and Amikacin hydrate

List of protein-ligand interactions

PDB code: **6W61** Ligand: **Amikacin hydrate (AMK)**

Hydrogen bonds

<----- A T O M 1 -----> <----- A T O M 2 ----->

	Atom no.	Atom name	Res name	Res no.	Chain		Atom no.	Atom name	Res name	Res no.	Chain	Distance
1.	1637	OD1	ASP	6900	A	<--	6684	N4	AMK	900		2.63
2.	5877	O	ILE	4334	B	<--	6695	O12	AMK	900		2.74
3.	5967	O	LYS	4340	B	<--	6663	O2	AMK	900		2.98
4.	5967	O	LYS	4340	B	<--	6665	O3	AMK	900		2.92
5.	5989	O	GLY	4341	B	<--	6676	N2	AMK	900		3.30

Non-bonded contacts

<----- A T O M 1 -----> <----- A T O M 2 ----->

	Atom no.	Atom name	Res name	Res no.	Chain		Atom no.	Atom name	Res name	Res no.	Chain	Distance
1.	1636	CG	ASP	6900	A	---	6684	N4	AMK	900		3.21
2.	1637	OD1	ASP	6900	A	---	6683	C16	AMK	900		3.82
3.	1637	OD1	ASP	6900	A	---	6684	N4	AMK	900		2.63
4.	1638	OD2	ASP	6900	A	---	6684	N4	AMK	900		3.22
5.	1673	CG1	VAL	6902	A	---	6683	C16	AMK	900		3.85
6.	5793	O	TYR	4329	B	---	6685	O9	AMK	900		3.60
7.	5812	CA	CYS	4330	B	---	6685	O9	AMK	900		3.75
8.	5814	O	CYS	4330	B	---	6680	C14	AMK	900		3.38
9.	5814	O	CYS	4330	B	---	6685	O9	AMK	900		3.45
10.	5858	CA	HIS	4333	B	---	6685	O9	AMK	900		3.61
11.	5860	O	HIS	4333	B	---	6694	O11	AMK	900		3.55
12.	5863	ND1	HIS	4333	B	---	6682	C15	AMK	900		3.59
13.	5863	ND1	HIS	4333	B	---	6683	C16	AMK	900		3.64
14.	5876	C	ILE	4334	B	---	6686	C17	AMK	900		3.79
15.	5876	C	ILE	4334	B	---	6695	O12	AMK	900		3.48
16.	5877	O	ILE	4334	B	---	6686	C17	AMK	900		3.84
17.	5877	O	ILE	4334	B	---	6687	C18	AMK	900		3.68
18.	5877	O	ILE	4334	B	---	6695	O12	AMK	900		2.74
19.	5898	CG	ASP	4335	B	---	6693	N5	AMK	900		3.78
20.	5899	OD1	ASP	4335	B	---	6686	C17	AMK	900		3.29
21.	5899	OD1	ASP	4335	B	---	6687	C18	AMK	900		3.70
22.	5899	OD1	ASP	4335	B	---	6693	N5	AMK	900		2.61
23.	5911	ND1	HIS	4336	B	---	6676	N2	AMK	900		3.89
24.	5913	CE1	HIS	4336	B	---	6671	C9	AMK	900		3.36
25.	5913	CE1	HIS	4336	B	---	6676	N2	AMK	900		3.64
26.	5966	C	LYS	4340	B	---	6663	O2	AMK	900		3.78
27.	5967	O	LYS	4340	B	---	6657	C1	AMK	900		3.76
28.	5967	O	LYS	4340	B	---	6662	C5	AMK	900		3.37
29.	5967	O	LYS	4340	B	---	6663	O2	AMK	900		2.98
30.	5967	O	LYS	4340	B	---	6665	O3	AMK	900		2.92
31.	5989	O	GLY	4341	B	---	6662	C5	AMK	900		3.76
32.	5989	O	GLY	4341	B	---	6676	N2	AMK	900		3.30

33.	5993	N	PHE	4342	B	---	6663	O2	AMK	900	3.60
34.	5994	CA	PHE	4342	B	---	6663	O2	AMK	900	3.55
35.	5997	CB	PHE	4342	B	---	6663	O2	AMK	900	3.74
36.	6013	N	CYS	4343	B	---	6676	N2	AMK	900	3.43
37.	6017	CB	CYS	4343	B	---	6676	N2	AMK	900	3.32
Number of hydrogen bonds: 5											
Number of non-bonded contacts: 37											

Supplementary Table-6 List of protein-ligand interaction between Methyl transferase and Geneticin

PDB code: 6W61 Ligand: Geneticin (GEN)											
Hydrogen bonds											

<----- A T O M 1 ----->						<----- A T O M 2 ----->					
	Atom no.	Atom name	Res name	Res no.	Chain		Atom no.	Atom name	Res name	Res no.	Chain	Distance
1.	1637	OD1	ASP	6900	A	<--	6687	O8	GEN	900		2.66
2.	1646	O	PHE	6901	A	<--	6688	O9	GEN	900		2.89
3.	5860	O	HIS	4333	B	<--	6671	N2	GEN	900		3.08
4.	5899	OD1	ASP	4335	B	<--	6665	N1	GEN	900		2.74
Non-bonded contacts											

<----- A T O M 1 ----->						<----- A T O M 2 ----->					
	Atom no.	Atom name	Res name	Res no.	Chain		Atom no.	Atom name	Res name	Res no.	Chain	Distance
1.	1636	CG	ASP	6900	A	---	6676	C12	GEN	900		3.59
2.	1636	CG	ASP	6900	A	---	6681	N4	GEN	900		3.54
3.	1636	CG	ASP	6900	A	---	6687	O8	GEN	900		3.18
4.	1637	OD1	ASP	6900	A	---	6676	C12	GEN	900		3.38
5.	1637	OD1	ASP	6900	A	---	6680	C15	GEN	900		3.34
6.	1637	OD1	ASP	6900	A	---	6681	N4	GEN	900		3.80
7.	1637	OD1	ASP	6900	A	---	6685	C18	GEN	900		3.54
8.	1637	OD1	ASP	6900	A	---	6687	O8	GEN	900		2.66
9.	1638	OD2	ASP	6900	A	---	6676	C12	GEN	900		3.16

10.	1638	OD2	ASP	6900	A	---	6681	N4	GEN	900	2.86
11.	1638	OD2	ASP	6900	A	---	6687	O8	GEN	900	3.54
12.	1643	N	PHE	6901	A	---	6687	O8	GEN	900	3.66
13.	1645	C	PHE	6901	A	---	6687	O8	GEN	900	3.57
14.	1645	C	PHE	6901	A	---	6688	O9	GEN	900	3.54
15.	1646	O	PHE	6901	A	---	6685	C18	GEN	900	3.63
16.	1646	O	PHE	6901	A	---	6687	O8	GEN	900	3.49
17.	1646	O	PHE	6901	A	---	6688	O9	GEN	900	2.89
18.	1663	N	VAL	6902	A	---	6688	O9	GEN	900	3.74
19.	1665	CA	VAL	6902	A	---	6688	O9	GEN	900	3.48
20.	1673	CG1	VAL	6902	A	---	6688	O9	GEN	900	3.48
21.	5793	O	TYR	4329	B	---	6662	O2	GEN	900	3.90
22.	5858	CA	HIS	4333	B	---	6661	C4	GEN	900	3.80
23.	5858	CA	HIS	4333	B	---	6666	O3	GEN	900	3.62
24.	5859	C	HIS	4333	B	---	6661	C4	GEN	900	3.58
25.	5859	C	HIS	4333	B	---	6671	N2	GEN	900	3.77
26.	5860	O	HIS	4333	B	---	6661	C4	GEN	900	3.74
27.	5860	O	HIS	4333	B	---	6667	C7	GEN	900	3.86
28.	5860	O	HIS	4333	B	---	6671	N2	GEN	900	3.08
29.	5861	CB	HIS	4333	B	---	6666	O3	GEN	900	3.58
30.	5861	CB	HIS	4333	B	---	6681	N4	GEN	900	3.55
31.	5862	CG	HIS	4333	B	---	6681	N4	GEN	900	3.32
32.	5863	ND1	HIS	4333	B	---	6676	C12	GEN	900	3.79
33.	5863	ND1	HIS	4333	B	---	6680	C15	GEN	900	3.31
34.	5863	ND1	HIS	4333	B	---	6681	N4	GEN	900	3.23
35.	5863	ND1	HIS	4333	B	---	6687	O8	GEN	900	3.28
36.	5865	CE1	HIS	4333	B	---	6680	C15	GEN	900	3.81
37.	5865	CE1	HIS	4333	B	---	6681	N4	GEN	900	3.84
38.	5865	CE1	HIS	4333	B	---	6687	O8	GEN	900	3.26
39.	5877	O	ILE	4334	B	---	6657	C1	GEN	900	3.69
40.	5877	O	ILE	4334	B	---	6662	O2	GEN	900	3.71
41.	5899	OD1	ASP	4335	B	---	6660	C3	GEN	900	3.73
42.	5899	OD1	ASP	4335	B	---	6664	C6	GEN	900	3.76
43.	5899	OD1	ASP	4335	B	---	6665	N1	GEN	900	2.74
44.	5911	ND1	HIS	4336	B	---	6682	C16	GEN	900	3.75
45.	5913	CE1	HIS	4336	B	---	6674	C11	GEN	900	3.89
46.	5913	CE1	HIS	4336	B	---	6682	C16	GEN	900	3.51
47.	5967	O	LYS	4340	B	---	6684	C17	GEN	900	3.31
48.	5987	CA	GLY	4341	B	---	6684	C17	GEN	900	3.89
49.	5988	C	GLY	4341	B	---	6678	N3	GEN	900	3.87
50.	5988	C	GLY	4341	B	---	6684	C17	GEN	900	3.68
51.	5989	O	GLY	4341	B	---	6672	C10	GEN	900	3.29
52.	5989	O	GLY	4341	B	---	6677	C13	GEN	900	3.88
53.	5989	O	GLY	4341	B	---	6678	N3	GEN	900	3.06
54.	5989	O	GLY	4341	B	---	6682	C16	GEN	900	3.26
55.	5989	O	GLY	4341	B	---	6684	C17	GEN	900	3.25
56.	6013	N	CYS	4343	B	---	6682	C16	GEN	900	3.72
57.	6017	CB	CYS	4343	B	---	6682	C16	GEN	900	3.60

Number of hydrogen bonds: 4

Number of non-bonded contacts: 57

Supplementary Table-7. The various components of the Binding Free Energy (kcal mol^{-1}) evaluated by Molecular Mechanics/Generalized Borne Surface Area (MM/GBSA) method for Rutin-RDRP complex during the simulation.

	Complex		Receptor		Ligand		Delta	
	Average	Std. Dev. (±)	Average	Std. Dev. (±)	Average	Std. Dev. (±)	Average	Std. Dev. (±)
VDW	-9483.16	46.17	-9434.92	46.33	-8.55	1.69	-39.69	4.48
ELE	-81612.70	140.16	-81362.80	139.02	-98.01	6.70	-151.88	8.48
GB	-11797.20	91.27	-11876.70	92.40	-79.61	4.31	159.14	7.99
GBSUR	373.51	2.89	375.88	2.81	5.04	0.03	-7.40	0.25
GAS	-91095.80	134.67	-90797.70	133.48	-106.55	6.97	-191.58	7.45
GBSOL	-11423.70	90.71	-11500.80	91.87	-74.58	4.31	151.73	7.99
GBTOT	-102520.00	88.20	-102299.00	86.07	-181.13	4.34	**-39.84**	3.78

Supplementary Table-8. The various components of the Binding Free Energy (kcal mol^{-1}) evaluated by Molecular Mechanics/Generalized Borne Surface Area (MM/GBSA) method for Silymarin-Exoribonuclease complex during the simulation.

	Complex		Receptor		Ligand		Delta	
	Average	Std. Dev. (±)	Average	Std. Dev. (±)	Average	Std. Dev. (±)	Average	Std. Dev. (±)
VDW	-4139.28	23.67	-4106.96	23.32	-4.15	1.45	-28.17	2.25
ELE	-36626.90	72.19	-36656.80	71.84	62.45	2.70	-32.58	3.72
GB	-5468.06	49.27	-5471.71	49.20	-48.01	1.38	51.65	3.02
GBSUR	189.61	1.35	189.56	1.33	4.18	0.03	-4.13	0.24
GAS	-4991.27	84.56	-4914.58	84.46	-15.94	5.67	-60.75	3.81
GBSOL	-5278.45	49.03	-5282.15	48.94	-43.82	1.38	47.52	3.02
GBTOT	-10269.70	73.97	-10196.70	73.50	-59.76	5.51	**-13.23**	2.21

Supplementary Table-9. The various components of the Binding Free Energy (kcal mol^{-1}) evaluated by Molecular Mechanics/Generalized Borne Surface Area (MM/GBSA) method for Luteolin-Helicase complex during simulation.

	Complex		Receptor		Ligand		Delta	
	Average	Std. Dev. (±)	Average	Std. Dev. (±)	Average	Std. Dev. (±)	Average	Std. Dev. (±)
VDW	-4517.20	31.98	-4487.37	31.47	0.13	1.44	-29.96	2.99
ELE	-39784.10	78.42	-39851.60	74.94	116.33	4.68	-48.87	5.48
GB	-6345.41	53.98	-6363.19	51.78	-35.29	2.32	53.07	4.78
GBSUR	212.37	1.79	214.14	1.80	2.73	0.01	-4.50	0.10
GAS	-44301.30	77.46	-44339.00	74.56	116.46	4.54	-78.83	5.35

GBSOL	-6133.04	53.65	-6149.06	51.45	-32.56	2.32	48.58	4.71
GBTOT	-50434.40	57.23	-50488.00	57.00	83.90	3.26	**-30.26**	2.15

Supplementary Table-10. The various components of the Binding Free Energy (kcal mol^{-1}) evaluated by Molecular Mechanics/Generalized Borne Surface Area (MM/GBSA) method for Amikacin hydrate-methyltransferase complex during simulation.

	Complex		Receptor		Ligand		Delta	
	Average	Std. Dev. (±)	Average	Std. Dev. (±)	Average	Std. Dev. (±)	Average	Std. Dev. (±)
VDW	-3210.18	19.60	-3172.04	18.80	-14.87	1.62	-23.28	3.58
ELE	-30120.00	73.37	-29663.10	62.87	-80.67	9.29	-376.26	36.51
GB	-4338.66	51.47	-4203.92	40.61	-520.33	4.78	385.60	34.39
GBSUR	144.55	1.11	143.98	1.12	5.31	0.07	-4.74	0.20
GAS	-33330.20	71.93	-32835.10	62.94	-95.54	9.82	-399.53	35.19
GBSOL	-4194.11	51.13	-4059.95	40.42	-515.03	4.78	380.86	34.28
GBTOT	-37524.30	44.69	-36895.00	44.22	-610.57	7.62	**-18.67**	4.73

Supplementary Table-11. The various components of the Binding Free Energy (kcal mol^{-1}) evaluated by Molecular Mechanics/Generalized Borne Surface Area (MM/GBSA) method for Geneticin-methyltransferase complex during simulation.

	Complex		Receptor		Ligand		Delta	
	Average	Std. Dev. (±)	Average	Std. Dev. (±)	Average	Std. Dev. (±)	Average	Std. Dev. (±)
VDW	-3237.24	20.19	-3198.67	20.06	-10.02	1.91	-28.55	3.53
ELE	-30222.50	55.56	-29785.90	53.82	32.18	8.41	-468.75	15.89
GB	-4295.45	43.22	-4219.32	41.35	-545.66	4.67	469.53	14.12
GBSUR	142.06	1.31	142.55	1.34	4.45	0.04	-4.94	0.14
GAS	-33459.70	54.67	-32984.60	54.90	22.16	7.75	-497.30	14.81
GBSOL	-4153.40	42.93	-4076.77	40.98	-541.21	4.66	464.59	14.09
GBTOT	-37613.10	33.71	-37061.40	34.58	-519.05	4.88	**-32.71**	3.55

Electrostatic energy (**ELE**); van der Waals contribution (**VDW**); total gas phase energy (**GAS**); nonpolar contribution to the solvation free energy (**GBSUR**); the electrostatic contribution to the solvation free energy (**GB**); sum of nonpolar and polar contributions to solvation (**GBSOL**); final estimated binding free energy (**GBTOT**).

Supplementary Table-12. Toxicity profile of 20 selected compounds.

Name of the compound	AMES Toxicity	hERG 1 Inhibitor	hERG 2 Inhibitor
Rutin Hydrate	NO	NO	YES
Silymarin	NO	NO	YES
Quercetin	NO	NO	NO
Mitoxantrone 2HCL	NO	NO	YES
Luteolin	NO	NO	NO
Aloin	NO	NO	NO
Morin Hydrate	NO	NO	NO
Kaempferol	NO	NO	NO
Madecassoside	NO	NO	YES
Amikacin Hydrate	NO	NO	NO
Geneticin	NO	NO	NO
Netilmicin Sulfate	NO	NO	NO
Hygromycin B	NO	NO	NO
Acarbose	NO	NO	YES
Apigenin	NO	NO	NO
Hesperidin	NO	NO	YES
Neohesperidin	NO	NO	YES
Troxerutin	NO	NO	YES
Notoginsenoside R1	NO	NO	YES
Salvianolic acid B	NO	NO	NO

References

[1] Z. Jin, X. Du, Y. Xu, Y. Deng, M. Liu, Y. Zhao, B. Zhang, X. Li, L. Zhang, C. Peng, Y. Duan, J. Yu, L. Wang, K. Yang, F. Liu, R. Jiang, X. Yang, T. You, X. Liu, X. Yang, F. Bai, H. Liu, X. Liu, L.W. Guddat, W. Xu, G. Xiao, C. Qin, Z. Shi, H. Jiang, Z. Rao, H. Yang, Structure of M^{pro} from COVID-19 virus and discovery of its inhibitors, bioRxiv, (2020) 2020.2002.2026.964882.

[2] A.A.J.J.o.B.S. Elfiky, Dynamics, SARS-CoV-2 RNA dependent RNA polymerase (RdRp) targeting: An in silico perspective, (2020) 1-9.

[3] B. Naik, N. Gupta, R. Ojha, S. Singh, V.K. Prajapati, D. Prusty, High throughput virtual screening reveals SARS-CoV-2 multi-target binding natural compounds to lead instant therapy for COVID-19 treatment, International journal of biological macromolecules, 160 (2020) 1-17.
[4] J.A. Tanner, B.-J. Zheng, J. Zhou, R.M. Watt, J.-Q. Jiang, K.-L. Wong, Y.-P. Lin, L.-Y. Lu, M.-L. He, H.-F.J.C. Kung, biology, The adamantane-derived bananins are potent inhibitors of the helicase activities and replication of SARS coronavirus, 12 (2005) 303-311.
[5] M.U. Mirza, M. Froeyen, Structural elucidation of SARS-CoV-2 vital proteins: Computational methods reveal potential drug candidates against main protease, Nsp12 polymerase and Nsp13 helicase, Journal of Pharmaceutical Analysis, 10 (2020) 320-328.
[6] Y. Ma, L. Wu, N. Shaw, Y. Gao, J. Wang, Y. Sun, Z. Lou, L. Yan, R. Zhang, Z. Rao, Structural basis and functional analysis of the SARS coronavirus nsp14–nsp10 complex, Proceedings of the National Academy of Sciences, 112 (2015) 9436.
[7] A. Chandra, V. Gurjar, I. Qamar, N. Singh, Identification of potential inhibitors of SARS-COV-2 endoribonuclease (EndoU) from FDA approved drugs: a drug repurposing approach to find therapeutics for COVID-19, Journal of Biomolecular Structure and Dynamics, (2020) 1-11.
[8] Y. Kim, R. Jedrzejczak, N.I. Maltseva, M. Wilamowski, M. Endres, A. Godzik, K. Michalska, A. Joachimiak, Crystal structure of Nsp15 endoribonuclease NendoU from SARS-CoV-2, 29 (2020) 1596-1605.
[9] K. Sharma, S. Morla, A. Goyal, S. Kumar, Computational guided drug repurposing for targeting 2'-O-ribose methyltransferase of SARS-CoV-2, Life Sci, 259 (2020) 118169-118169.
[10] A.C. Walls, Y.J. Park, M.A. Tortorici, A. Wall, A.T. McGuire, D. Veesler, Structure, Function, and Antigenicity of the SARS-CoV-2 Spike Glycoprotein, Cell, 181 (2020) 281-292.e286.
[11] Q. Wang, Y. Zhang, L. Wu, S. Niu, C. Song, Z. Zhang, G. Lu, C. Qiao, Y. Hu, K.Y. Yuen, Q. Wang, H. Zhou, J. Yan, J. Qi, Structural and Functional Basis of SARS-CoV-2 Entry by Using Human ACE2, Cell, 181 (2020) 894-904.e899.
[12] M.U. Mirza, S. Ahmad, I. Abdullah, M. Froeyen, Identification of novel human USP2 inhibitor: might involve in SARS-CoV-2 papain-like (PLpro) protease deubiquitination activity, (2020).
[13] S. Kang, M. Yang, Z. Hong, L. Zhang, Z. Huang, X. Chen, S. He, Z. Zhou, Z. Zhou, Q. Chen, Y. Yan, C. Zhang, H. Shan, S. Chen, Crystal structure of SARS-CoV-2 nucleocapsid protein RNA

binding domain reveals potential unique drug targeting sites, Acta pharmaceutica Sinica. B, 10 (2020) 1228-1238.