Supplementary Material for

Virtual Screening-Driven Drug Discovery of SARS-CoV2 Enzyme Inhibitors Targeting Viral Attachment, Replication, Post-Translational Modification and Host Immunity Evasion Infection Mechanisms

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Altertoxin V (1) [1]





Altertoxin II (2) [1]

0

ΗΟ

Chloropupukeanolide A (6) [1]



Penicillixanthone A (3) [1]



Phomasetin (7) [1]

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Isochaetochromin D1 (8) [1]



Arisugacin A (12) [2]



Scequinadoline A (16) [3]





















Pulvic Acid (25) [7]



Aspergilol H (R) (9) [1]



Aspernolide A (13) [2]



14S - oxoglyantrypine (17) [4]



Asperterrestide A (S) (21) [5]

Asperterrestide A (R) (22) [5]

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Rubrolide S (23) [6]

Isoaspulvinone E (24) [7]

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ő Quinadoline B (19) [4]

ΗN ő









Deoxynortryptoquivaline (18) [4]









όн Rhodatin (14) [1]



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Asperphenalenone A (26) [1]

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Stachybotrosin (31) [1]



HO

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Stachybotrysam A (27) [1]

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Periconiasin J (32) [1]



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HC

Stachybotrysam B (28) [1]

HO

OH



Stachybotrysam C (30) [1]

Brasilamide C (34) [1]



Enniatin B (38) [1]



Brasilamide D (35) [1]



Enniatin B1 (39) [1]



Enniatin A1 (40) [1]

С

óн



Asperginin C (37) [1]

(R)-Concentricolide (41) [1]





(S)-Concentricolide (42) [1]

Integracin A (43) [1]

Integracin B (44) [1]

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Brasilamide B (33) [1]





Tetrahydrophomasetin (49) [1]





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Equisetin (46) [1]







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Aspergilol I (54) [1]



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Cordyol C (56) [1]



Coccoquinone (55) [1]

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Integrastatin B (51) [1]

OH

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Halovir A (57) [1]

Halovir D (60) [1]



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Halovir B (58) [1]



òн HO



(S)-Isobutyrolactone II (62) [2]

(R)-Isobutyrolactone II (63) [2]

Balticolid (64) [10]

ΌH



Halovir E (61) [1]



Cytosporin Acid (53) [9]

Ĥ Ö

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Integric Acid (52) [8]

0 Ν́Η 0 HO ΗÑ











Vanitaracin A (65) [1]

(-)-2'R-1-hydroxyisorhodoptilometrin (66) [1]

Versicolactone (67) [11]

Butyrolactone IV (68) [11]



Hirsutine (69) [12]



Hippeastrine (70) [12]

HO

Homonojirimycin (71) [12]



Neoechinulin B (72) [12]





Hydroxyvittatine (73) [12]





Deoxytryptoquivaline (75) [1]

0F

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Stachyflin (76) [1]



Tryptoquivaline (77) [4]

ОН ö ΝH₂

Cladosin C (78) [13]

OH

Diorcinol (79) [14]

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(Z)-5-(Hydroxymenthyl)-2-(6') methylhept-2'-en-2'-yl)-phenol (80) [14]

ΟН HO НÓ

Aspulvinone E (81) [7]

Emerimidine A (82) [15]

HO

HC

Emerimidine B (83) [15]



TAN-931 (87) [16]

HO OH

Purpurquinone B (84) [16]



Sorbicathechol A (88) [17]

HO ÓН

Purpurquinone C (85) [16]

Purpurester A (86) [16]

OH

HO

HO

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Figure S1. Structures of the antiviral fungal natural products **1–97** docked against five SARS-CoV2 proteins.

	Antiviral	Binding Energy (kcal/mol)					
Cpd	Activity	PLpro	RdRP	CLpro	CLpro (blind)	nsp15	S Protein
1	Anti-HIV	-9.4	-8.5	-7.2	-8.1	-8.1	-7.1
2	Anti-HIV	-9.2	-8.3	-7.5	-8.4	-7.6	-7.6
3	Anti-HIV	-9.5	-8.1	-8.2	-8.3	-6.7	-8.1
4	Anti-HIV	-10.3	-9.6	-7.9	-7.9	-8.5	-8.1
5	Anti-HIV	-9.5	-7.8	-6.5	-7.3	-7.8	-7.1
6	Anti-HIV	-10.0	-7.7	-7.5	-8.8	-6.8	-8.1
7	HIV-1 Integrase Inhibitor	-9.6	-6.9	-7.2	-7.2	-6.9	-8.3
8	HIV-1 Integrase Inhibitor	-9.9	-8.4	-7.9	-8.3	-9.1	-9.5
9	Anti Herpes simplex	-9.6	-7.6	-7.9	-7.7	-8.2	-9.1
10	Anti Herpes simplex	-9.2	-7.7	-8.3	-8.2	-8.1	-9.2
11	Anti Herpes simplex	-8.9	-9.1	-8.9	-8.9	-8.4	-10.2
12	Anti Herpes simplex	-10.0	-8.5	-8.0	-8.0	-8.5	-9.2
13	Anti Herpes simplex	-9.2	-7.5	-7.1	-7.6	-7.5	-9.3
14	Anti Hep C	-9.0	-7.9	-7.1	-7.3	-7.9	-9.9
15	Anti Hep C	-10.9	-9.2	-8.6	-8.5	-8.9	-9.4
16	Anti Hep C	-9.1	-9.1	-8.7	-9.5	-7.9	-8.5
17	Anti-influenza	-9.6	-8.3	-8.4	-8.3	-7.4	-7.6
18	Anti-influenza	-9.6	-7.4	-7.6	-7.7	-7.1	-8.0
19	Anti-influenza	-10.6	-9.8	-8.3	-9.5	-9.1	-10.5
20	Anti-influenza	-10.9	-8.5	-8.1	-8.7	-8.6	-8.3
21	Anti-influenza	-8.9	-7.6	-8.3	-8.2	-7.3	-8.7
22	Anti-influenza	-8.9	-7.6	-8.4	-7.3	-7.4	-9.7
23	Anti-influenza	-8.8	-7.4	-7.7	-8.2	-7.8	-10.3
24	Anti-influenza	-7.7	-7.1	-7.4	-7.5	-8.6	-9.7
25	Anti-influenza	-7.9	-7.5	-6.6	-7.2	-8.5	-9.3
26	Anti-HIV	-8.6	-6.6	-7.0	-6.5	-6.6	-5.5
27	Anti-HIV	-8.2	-8.1	-6.9	-7.2	-6.0	-6.4
28	Anti-HIV	-6.8	-6.3	-5.9	-6.4	-6.6	-5.6
29	Anti-HIV	-8.2	-7.5	-5.6	-6.8	-6.9	-5.5
30	Anti-HIV	-7.6	-7.5	-6.0	-7.0	-5.5	-6.5
31	Anti-HIV	-8.5	-7.5	-6.5	-7.5	-6.4	-7.1
32	Anti-HIV	-8.5	-7.8	-6.7	-7.5	-5.9	-7.4
33	Anti-HIV	-8.1	-6.6	-6.3	-6.9	-6.5	-5.9
34	Anti-HIV	-7.0	-6.3	-5.8	-5.9	-5.9	-5.6
35	Anti-HIV	-7.4	-6.6	-6.4	-6.6	-6.2	-5.9

Table S1. Docking results of antiviral fungal natural products 1–97 against SARS-CoV2 proteins.

36	Anti-HIV	-8.2	-7.3	-6.9	-7.0	-5.2	-7.6
37	Anti-HIV	-8.7	-7.3	-7.5	-7.8	-6.8	-6.7
38	Anti-HIV	-7.3	-7.2	-6.2	-6.3	-5.4	-6.0
39	Anti-HIV	-7.3	-7.6	-6.1	-6.3	-5.3	-6.2
40	Anti-HIV	-7.3	-6.9	-5.9	-6.1	-5.8	-4.7
41	Anti-HIV	-6.7	-6.2	-5.7	-5.9	-5.3	-5.5
42	Anti-HIV	-6.6	-5.9	-5.5	-6.1	-5.5	-5.3
43	HIV-1 Integrase Inhibitor	-7.3	-5.5	-5.4	-6.1	-5.7	-7.5
44	HIV-1 Integrase Inhibitor	-7.2	-6.0	-5.9	-6.1	-6.0	-7.7
45	HIV-1 Integrase Inhibitor	-7.4	-5.9	-5.9	-6.2	-5.8	-7.7
46	HIV-1 Integrase Inhibitor	-7.4	-6.9	-6.2	-6.3	-6.7	-7.5
47	Inhibitor	-8.0	-6.6	-6.3	-6.3	-6.8	-8.4
48	Inhibitor	-8.3	-6.9	-6.5	-6.5	-6.1	-8.7
49	Inhibitor HIV-1 Integrase	-7.9	-7.2	-5.8	-6.4	-5.7	-7.9
50	Inhibitor HIV-1 Integrase	-8.0	-7.3	-6.8	-6.9	-5.9	-7.8
51	Inhibitor HIV-1 Integrase	-8.1	-7.2	-6.7	-7.1	-6.5	-7.8
52	Inhibitor HIV-1 Integrase	-7.5	-6.0	-6.4	-6.3	-6.5	-7.9
53	Inhibitor Anti Herpes	-7.2	-6.3	-5.7	-5.8	-5.2	-6.8
54	simplex Anti Herpes	-8.0	-7.5	-0.8	-7.1	-0.5	-8.0
56	simplex Anti Herpes	-6.9	-6.5	-5.5	-6.6	-6.2	-0.4
50	simplex Anti Herpes	-0.9	-0.5	-5.5	-0.0	-0.2	-7.5
58	simplex Anti Herpes	-0.8	-0.4	5.8	-5.0	-5.0	-5.0
50	simplex Anti Herpes	7.5	-0.5	-5.0	-0.1	62	-0.0
60	simplex Anti Herpes	-7.3	-6.5	-5.9	-5.2	-6.1	-5.5
61	simplex Anti Herpes	-7.1	-6.3	-6.0	-5.9	-6.2	-53
62	simplex Anti Herpes	-7.9	-6.6	-6.7	-6.7	-6.9	-8.3
63	simplex Anti Herpes simplex	-7.7	-6.5	-7.2	-6.8	-6.9	-7.9

64	Anti Herpes	-7.4	-6.2	-5.3	-6.0	-5.4	-6.6
	simplex	0.0		-			
65	HBV	-8.0	-7.1	-7.0	-/.1	-6.4	-9.0
66		-/.0	-1.3	-6.9	-7.2	-6.8	-8.9
67	Anti-Tobacco Mosaic Virus	-8.3	-7.8	-6.6	-6.4	-6.6	-9.1
68	Anti-Tobacco Mosaic Virus	-8.4	-8.1	-7.2	-7.9	-6.5	-9.0
69	Anti-Influenza	-8.3	-7.0	-6.0	-6.8	-6.3	-6.1
70	Anti-Influenza	-8.3	-7.5	-7.4	-7.3	-6.9	-6.7
71	Anti-influenza	-6.0	-4.6	-4.3	-4.8	-5.0	-4.6
72	Anti-influenza	-8.4	-6.9	-6.5	-7.4	-6.4	-6.9
73	Anti-Influenza	-8.1	-7.2	-6.5	-6.5	-6.3	-6.1
74	Anti-influenza	-8.2	-7.1	-7.6	-7.6	-6.3	-6.8
75	Anti-influenza	-7.8	-7.7	-7.0	-7.5	-6.7	-7.7
76	Anti-influenza	-8.7	-8.2	-7.4	-8.1	-7.9	-6.9
77	Anti-influenza	-8.4	-8.2	-7.1	-7.5	-7.6	-7.2
78	Anti-influenza	-6.7	-6.1	-5.5	-5.9	-5.6	-5.1
79	Anti-influenza	-6.7	-6.3	-5.4	-6.5	-6.3	-6.0
80	80 Anti-influenza		-5.7	-5.6	-5.6	-5.2	-7.3
81	Anti-influenza	-7.7	-6.7	-7.4	-7.5	-6.9	-8.8
82	Anti-influenza	-6.0	-5.4	-5.4	-5.2	-5.2	-6.5
83	Anti-influenza	-5.9	-5.9	-5.0	-5.3	-5.3	-6.5
84	Anti-influenza	-9.0	-7.3	-7.4	-7.6	-6.8	-8.8
85	Anti-influenza	-8.5	-7.6	-7.7	-7.3	-6.9	-8.7
86	Anti-influenza	-6.6	-5.7	-5.5	-6.3	-5.6	-6.8
87	Anti-influenza	-7.4	-6.4	-6.7	-6.5	-6.2	-7.7
88	Anti-influenza	-8.4	-7.2	-6.5	-6.6	-6.6	-7.7
89	Anti-influenza	-8.2	-7.9	-6.9	-7.1	-6.1	-8.3
90	Anti-influenza	-8.3	-7.3	-7.0	-6.7	-6.2	-8.3
91	Anti-influenza	-8.0	-7.0	-6.5	-7.1	-5.9	-7.7
92	Anti-influenza	-8.5	-7.5	-6.3	-6.9	-5.6	-8.0
93	Anti-enterovirus	-7.1	-6.4	-6.1	-7.0	-5.5	-7.8
94	94 Anti-enterovirus		-6.5	-6.2	-6.3	-5.4	-7.4
95	95 Anti-enterovirus		-6.8	-6.5	-6.9	-6.1	-8.0
96	96 Anti-enterovirus		-7.4	-6.1	-6.4	-5.6	-7.3
97	Anti-enterovirus	-8.8	-6.9	-7.5	-8.2	-6.9	-8.5
Lopinavir [20]	Antiretroviral	-6.9	-	-7.6	-	-	-
Favipiravir-RTP [20]	Anti-influenza	-	-7.6	-	-	-	-
Benzopurpurin B	Anti- endoribonuclease	-	-	-	-	-9.4	-
Umifenovir [20]	Anti-influenza	-	-	-	-	-	-7.1

gainst SAF	RS-CoV2 pap	ain-like protease (PLpro).
Cpd	Binding Energy (kcal/mol)	Interacting Amino Acids (non-van der Waals)
3	-9.5	Ile330, Asp339, Leu557, Ile580, Arg586, Arg558, Val365, Lys711
4	-10.3	Val304, Ile310, Ala338, Ala579, Ile580, Val635, Lys711, Arg712, Leu741, Leu742

Leu557, Ala579, Ile580, Thr583, Met630, Arg712, Phe735, Leu742

Val304, Ile310, Ala338, His342, Leu557, Arg558, Ala579, Ile580, Arg

Ile227, Ala242, Leu330, Leu331, Ala333, Ile335, Phe336, Ala358,

Asp339, Arg345, Leu557, Arg558, Ala579, Ile580, Thr583, Arg586,

Asp339, Leu557, Arg558, Ile580, Thr583, Arg586, Tyr634, Val635,

Asp339, Leu557, Arg558, Ile580, Arg586, Met630, Ser660, Arg712

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-10.0

-10.9

-9.6

-9.6

-10.6

-10.9

712, Phe735

Val358, Phe360, Leu364

Lys694, Lys711, Leu742

Ile310, Lys711, Arg712

Tyr634, Val635, Lys711, Arg712

His342, Leu557, Ala579, Lys711, Arg712

His342, Arg345, Leu557, Met630, Val635, Lys711

His342, Met560, Thr583, Lys711, Arge712, Phe735,

Arg345, Leu557, Ala579, Ile580, Lys711, Arg712

Table S2. Molecular docking scores and binding site interactions of the top-ranked compounds as

Cpd	Binding Energy (kcal/mol)	Interacting Amino Acids (non-van der Waals)
3	-8.2	Thr25, Thr26, His41, Met49, Cys145, His163, Gln189
4	-7.9	His41, Met165
8	-7.9	His41, Phe140, Cys145, Glu166
9	-7.9	Thr25, His41, Met49, Cys145, Arg188
10	-8.3	His41, Met49, Cys145, Met165, Gln189
11	-8.9	Thr26, His41, Met165, Gln192
12	-8.0	Thr26, His41, Gly143, Cys145, Glu199
15	-8.6	His41, Met49, Cys145, Met165, Gln189
16	-8.7	His41, Met49, Asn142, Gly143, Met165
17	-8.4	His41, Met49, Leu141, Cys145, Glu166
19	-8.3	His41, Met49, Asn142, Gly143, Glu166
20	-8.1	His41, Met49, Gln189
21	-8.3	His41, Leu141, Asn142, Met165, Gln189
22	-8.4	His41, Leu141, Asn142, Met165, Gln189

Table S3. Molecular docking scores and binding site interactions of top-ranked compounds againstSARS-CoV2 chymotrypsin-like protease (3CLpro).

Cpd	Binding Energy (kcal/mol)	Interacting Amino Acids (non-van der Waals)
1	-8.5	Ala125, Val128, His133, Leu240, Tyr728
2	-8.3	Thr565, Leu576, Asp684, Ala685
3	-8.1	Asn497, Arg569, Leu576, Lys577, Ala685, Thr687, Ala688, Tyr689
4	-9.6	Ile494, Lys500, Arg569, Leu576, Lys577, Ala580, Ser682, Tyr689
8	-8.4	Asp760, Asp761, Leu758, Cys813, Ser814
11	-9.1	Lys500, Leu576, Ala685
12	-8.5	Ile494, Asn497, Lys500, Arg569, Lys577, Ala685
15	-9.2	Ile589, Lys593, Leu758, Cys813
16	-9.1	Arg569, Asp684, Ala688, Ala685
17	-8.3	Arg569, Leu578, Lys577, Ala685
19	-9.8	Arg569, Gln573, Ala580, Ala685, Ala688, Tyr689
20	-8.5	Lys577, Ala580, Ile589, Ala685, Ala688

Table S4. Molecular docking scores and binding site interactions of top-ranked compounds against

 SARS-CoV2 RNA-directed RNA polymerase (RdRp).

Cpd	Binding Energy (kcal/mol)	Interacting Amino Acids (non-van der Waals)
1	-8.1	Leu201, Gln202, Tyr279
4	-8.5	His235, Gly247, Gly248, Val292, Tyr343, Leu346
8	-9.1	His250, Val292, Met331, Trp333, Tyr343, Lys345
9	-8.2	Tyr343, His235, His259, Lys290, Val292, Trp333, Glu340, Gln345, Leu346
10	-8.1	Leu252, Leu266, Asp268, Pro271, Asp273, Lys277, Tyr279, Asp297
11	-8.4	Ser294, Trp333, Lys335, Tyr343
12	-8.5	Gly248, Lys290, Trp333, His235, Tyr343, Pro344
15	-8.9	His235, His242, Gly247, Trp333, Thr341, Tyr343
19	-9.1	Lys290, Val292, Tyr343, Lys345, Leu346
20	-8.6	Met219, Phe241, Ser242, Tyr238, Glu261
24	-8.6	Leu252, Leu266, Thr275, Lys277, Asp297
25	-8.5	Trp333, His235, Tyr343, Gly248, His250, Lys290

Table S5. Molecular docking scores and binding site interactions of top-ranked compounds against SARS-CoV2 non-structural protein 15 (nsp15).

Cpd	Binding Energy (kcal/mol)	Interacting Amino Acids (non-van der Waals)
8	-9.5	Phe430, Arg431, Lys432, Ser433, Asn434, Thr444, Tyr447, Phe464
9	-9.1	Tyr395, Phe430, Asp441, Phe464, Pro465
10	-9.2	Phe430, Asrg431, Lys432, Asp441, Phe464, Pro465
11	-10.2	Tyr395, Phe430, Asn434, Asp441, Ala449, Pro465
12	-9.2	Tyr395, Phe430, Asp441, Ser443, Gly459
13	-9.3	Lys432, Ser433, Asp441, Tyr447, Ala449, Thr452, Val457
14	-9.9	Phe430, Asn434, Asp441, Tyr447, Ala449
15	-9.4	Phe430, Lys432, Tyr447, Ala449, Cys454, Pro465
19	-10.5	Phe430, Ser433, Asp441, Tyr447, Ala449, Cys454
22	-9.7	Phe430, Lys432, Tyr447, Ala449
23	-10.3	Asp441, Thr444, Glu445, Tyr447
24	-9.7	Ser433, Glu439, Asp441
25	-9.3	Ser433, Glu439, Asp441

Table S6. Molecular docking scores and binding site interactions of top-ranked compounds against

 SARS-CoV2 spike protein.

References

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