Supplementary Table SI. Standard precision (SP) molecular docking of SARS-CoV-2 Mpro with top 50 natural compounds from L1400 library of Selleck Inc.

S. No.	Name of compounds	Nature of the compound	Docking score [kcal/mol]	Glide g-score [kcal/mol]	Glide e-model [kcal/mol]	Glide energy [kcal/mol]
1	Polymyxin B	Antibiotic	–11.212	–11.236	–152.814	–88.071
2	Complanatuside	Flavonoid	–8.667	–8.672	–103.861	–74.223
3	Kaempferol-3-O-glucorhaMnoside	Flavonoid	–8.642	–8.717	–93.836	–67.147
4	Proanthocyanidin	Polyphenols	–8.513	–8.513	–91.259	–61.562
5	Typhaneoside	Flavonoid-3-o-glycosides	–8.350	–8.425	–95.466	–65.687
6	Amikacin	Antibiotic	–8.236	–8.408	–124.058	–75.963
7	Hederacoside D	Saponins	–7.915	–7.915	–98.653	–70.812
8	Thymopentin	Immunostimulant	–7.741	–8.030	–97.893	–62.710
9	Specnuezhenide	Ingredients of Chinese medicine	–7.686	–7.687	–92.232	–65.735
10	1,2,3,4,6-O-Pentagalloylglucose	Ester of glucose	–7.644	–8.188	–107.694	–76.130
11	Parishin A	Natural product	–7.628	–7.628	–100.862	–70.823
12	Isepamicin	Aminoglycoside antibiotic	–7.610	–7.792	–101.710	–55.975
13	Netilmicin	Aminoglycoside antibiotics	–7.559	–8.328	–103.437	–57.087
14	Azlocillin	Acylampicillin antibiotic	–7.516	–7.516	–76.238	–54.954
15	Naringenin	Flavonoid	–7.270	–7.318	–55.678	–38.884
16	Sarafloxacin	Quinolone antibiotic	–7.256	–7.297	–70.159	–45.423
17	10-Hydroxy-camptothecin	Indole alkaloid	–7.141	–7.159	–64.678	–46.153
18	Cinchonine	Alkaloid	–7.073	–7.108	–59.588	–40.748
19	Daurisoline	Alkaloid	–6.960	–7.227	–88.021	–56.676
20	Paclitaxel	Anticancer medicine	–6.947	–6.951	–83.816	–60.998
21	Lycorine	Alkaloid	–6.883	–6.966	–59.820	–39.557
22	Oroxin B	Flavonoid	–6.879	–6.898	–85.265	–57.345
23	Tosufloxacin	Fluoroquinolone antibiotic	–6.844	–6.853	–66.704	–44.610
24	Halofuginone	Alkaloid derivative	–6.828	–6.854	–70.026	–47.192
25	Dracohodin	Extracted from Dragon blood	–6.790	–6.808	–57.552	–39.256
26	Galangin	Flavonoid	–6.743	–6.862	–51.265	–37.576
27	Tigecycline	Antibiotic	–6.704	–7.039	–90.316	–60.082
28	Sparteine	Alkaloid	–6.685	–6.733	–57.351	–34.457
29	Mezlocillin	Penicillin antibiotic	–6.649	–6.649	–76.826	–59.164
30	Nuciferine	Alkaloid	–6.509	–6.602	–53.015	–34.684
31	Icariin	Flavonoid	–6.494	–6.501	–74.989	–59.878
32	Epigoitrin	Alkaloid	–6.457	–6.457	–32.161	–22.789
33	Isosakuranetin	Flavanone	–6.456	–6.503	–51.432	–36.387
34	Tubeimoside I	Terpenoid	–6.438	–6.438	–72.261	–59.102
35	Pectolinarin	Natural anti-inflammatory compound	–6.429	–6.438	–82.760	–62.673
36	Stylopine	Alkaloid	–6.286	–6.440	–57.389	–38.297
37	Norisoboldine	Alkaloid	–6.278	–6.365	–56.265	–37.636
38	Docetaxel	Anticancerous medicine	–6.166	–6.171	–73.512	–55.484

Supplementary Table SI. Cont.

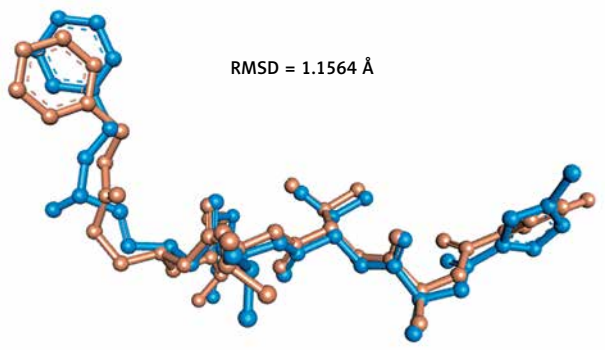
S. No.	Name of compounds	Nature of the compound	Docking score [kcal/mol]	Glide g-score [kcal/mol]	Glide e-model [kcal/mol]	Glide energy [kcal/mol]
39	Forchlorfenuron	Plant growth regulator	–6.147	–6.147	–48.372	–36.017
40	Scutellarein	Flavone	–6.132	–6.253	–52.378	–37.860
41	(-)-Epicatechin gallate	Flavonoid	–6.084	–6.261	–72.482	–54.519
42	Sparfloxacin	Fluoroquinolones (antibiotic)	–5.995	–6.012	–57.746	–41.640
43	Piperlongumine	Natural product (long pepper)	–5.985	–5.985	–51.366	–38.708
44	Myricetin	Flavonoid	–5.935	–6.037	–56.332	–43.530
45	Matrine	Alkaloid	–5.853	–5.855	–47.772	–32.797
46	Trecator	Antibiotic	–5.845	–5.846	–35.597	–26.116
47	Neomycin	Aminoglycoside antibiotic	–5.816	–7.019	–103.362	–57.295
48	Biochanin A	Monoflavonoid	–5.754	–5.829	–52.431	–38.873
49	Liensinine	Alkaloid	–5.604	–5.816	–77.632	–52.888
50	Kaempferide	Flavonol	–5.424	–5.534	–63.245	–49.275

Supplementary Table SII. Standard precision (SP) molecular docking of SARS-CoV-2 PLpro with top 50 natural compounds from L1400 library of Selleck Inc.

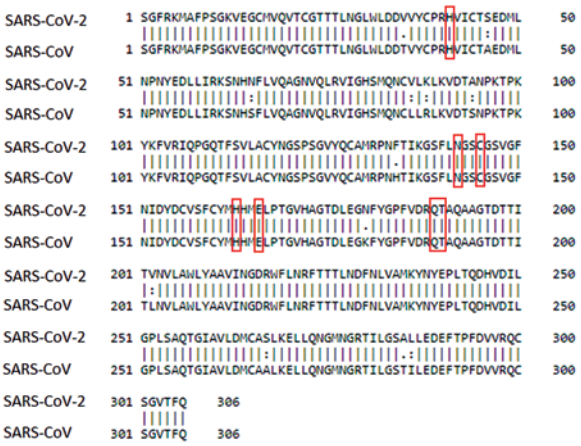
S. No.	Name of compounds	Nature of compounds	Docking score [kcal/mol]	Glide g-score [kcal/mol]	Glide e-model [kcal/mol]	Glide energy [kcal/mol]
1	Secoisolariciresinol diglucoside	Antioxidant phytoestrogen	–6.973	–6.973	–76.181	–59.119
2	Sophoricoside	Isoflavone	–6.403	–6.477	–55.728	–45.598
3	Eriocitrin	Flavanone-7-O-glycoside	–6.204	–6.215	–75.626	–55.826
4	(+)-Catechin	Natural phenol	–6.186	–6.186	–46.521	–34.584
5	Rhapontin	Glucoside	–6.182	–6.182	–57.016	–46.366
6	Nadide	Dinucleotide	–6.124	–6.126	–71.067	–48.557
7	Benzoylpaeoniflorin	Natural product	–5.997	–5.997	–61.594	–51.320
8	Cytisine	Alkaloid	–5.980	–5.981	–34.385	–24.702
9	Naringenin	Flavonoid	–5.957	–6.005	–44.403	–31.896
10	Yohimbine	Alkaloid	–5.875	–5.938	–39.950	–31.068
11	Apigenin	Flavone	–5.866	–5.967	–41.514	–31.231
12	4-Hydroxyquinazoline	Heterocyclic compound	–5.842	–5.890	–33.189	–23.924
13	(-)-Epicatechin	Natural phenol	–5.830	–5.830	–44.749	–33.664
14	Norcantharidin	Derivative of natural product	–5.789	–5.789	–33.507	–25.087
15	(+)-Gallocatechin	Flavan-3-ol	–5.782	–5.800	–46.411	–34.379
16	Isatin	Indole	–5.716	–5.716	–31.563	–22.743
17	Oxyresveratrol	Stillbenoid	–5.715	–5.726	–41.389	–30.426
18	Phloretin	Natural phenol	–5.691	–5.894	–46.470	–33.988
19	N-Ethylmaleimide	Organic compound	–5.676	–5.676	–28.492	–21.348
20	(-)-Epicatechin gallate	Flavonoid	–5.669	–5.846	–61.209	–50.003

Supplementary Table SII. Cont.

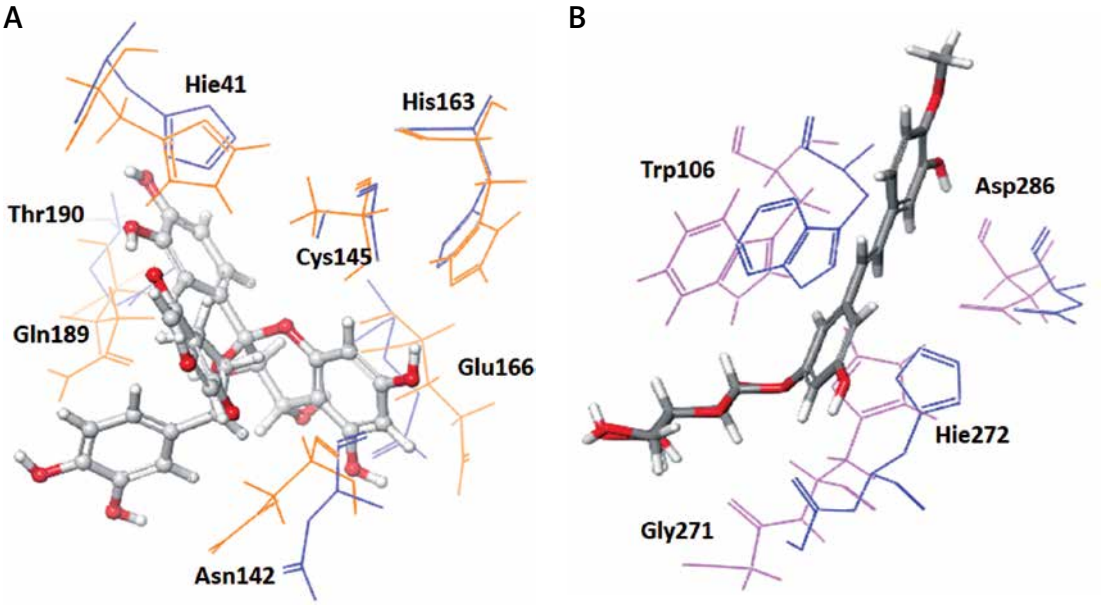
S. No.	Name of compounds	Nature of compounds	Docking score [kcal/mol]	Glide g-score [kcal/mol]	Glide e-model [kcal/mol]	Glide energy [kcal/mol]
21	Neohesperidin	Flavanone glycoside	–5.627	–5.638	–57.750	–44.917
22	Benzoyleneurea	Quinazolinedione	–5.624	–5.640	–32.964	–24.244
23	2-Benzoxazolinone	Phytoanticipin	–5.623	–5.636	–31.920	–23.118
24	Kynurenic acid	Metabolic product of L-Tryptophan	–5.607	–5.607	–35.762	–24.631
25	Eriodictyol	Flavonoid	–5.588	–5.636	–46.142	–35.240
26	Rhapontigenin	Stillbenoid	–5.578	–5.589	–41.829	–32.264
27	7-Hydroxy-3,4-dihydrocarbostyril	Synthetic quinoline compound	–5.547	–5.550	–34.225	–24.752
28	Echinatin	Licorice extract	–5.545	–5.721	–42.855	–32.305
29	Lawsone	Naphthoquinone	–5.528	–5.528	–34.827	–24.365
30	Indole-3-acetic acid	Plant hormone	–5.515	–5.516	–35.927	–23.890
31	Dihydrothymine	Intermediate product of thymine	–5.492	–5.492	–30.993	–23.351
32	Sophocarpine	Natural product	–5.475	–5.477	–36.052	–27.078
33	Umbelliferone	Product of coumarin family	–5.454	–5.481	–31.138	–22.523
34	Oxindole	Aromatic heterocyclic compound	–5.451	–5.451	–28.739	–21.204
35	Gallic acid	Phenolic acid	–5.448	–5.448	–35.003	–25.121
36	Daphnetin	Coumarin	–5.433	–5.481	–31.240	–23.824
37	Acetophenone	Aromatic ketone	–5.418	–5.418	–25.837	–19.858
38	Plumbagin	Naphthoquinone	–5.372	–5.397	–29.496	–23.785
39	Carvacrol	Monoterpene derivative	–5.363	–5.363	–28.024	–21.009
40	7-Hydroxyflavone	Flavonoid	–5.360	–5.394	–35.378	–26.261
41	Daidzein	Isoflavone	–5.356	–5.378	–34.025	–26.242
42	Apatinib	Tyrosine kinase inhibitor	–5.303	–5.388	–52.099	–43.433
43	Xanthurenic Acid	Intermediate of Vitamin B6	–5.295	–5.507	–36.791	–24.876
44	Paeoniflorin	Constituent of herbal medicine	–5.281	–5.281	–52.460	–42.792
45	Isopsoralen	Natural fluorocoumarin	–5.267	–5.267	–28.683	–21.699
46	4-Isopropyl benzaldehyde	Organic compound	–5.257	–5.257	–26.971	–20.429
47	Alizarin	Organic compound	–5.222	–5.323	–34.916	–26.463
48	Thymoquinone	Phytochemical compound	–5.201	–5.201	–29.229	–22.127
49	Juglone	Organic compound	–5.198	–5.241	–28.479	–23.189
50	4-Ketoisophorone	Component of saffron	–5.185	–5.185	–27.324	–20.868



Supplementary Figure S1. Validation of the docking procedure by measuring root mean square deviation (RMSD) between the crystal structure pose and docked pose of ligand (N3) co-crystallized with Mpro



Supplementary Figure S2. Pairwise sequence alignment of Mpro derived from SARS-CoV and SARS-CoV-2. The residues inside the box are involved in hydrogen bonds and hydrophobic interactions



Supplementary Figure S3. Superimposition of SARS-CoV-2 Mpro-proanthocyanidin (**A**), and SARS-CoV-2 PLpro-rhapontin (**B**) active sites with that of Mpro and PLpro from SARS-CoV. Amino acid residues depicted in purple and gold colors belong to Mpro of SARS-CoV and SARS-CoV-2, respectively. Similarly, amino acid residues depicted in magenta and blue colors belong to PLpro of SARS-CoV and SARS-CoV-2, respectively. Amino acid residues depicted in purple and gold belong to Mpro of SARS-CoV and SARS-CoV-2

Supplementary Figure S4. Pairwise sequence alignment of PLpro derived from SARS-CoV and SARS-CoV-2. The residues inside the box are involved in hydrogen bonds and hydrophobic interactions