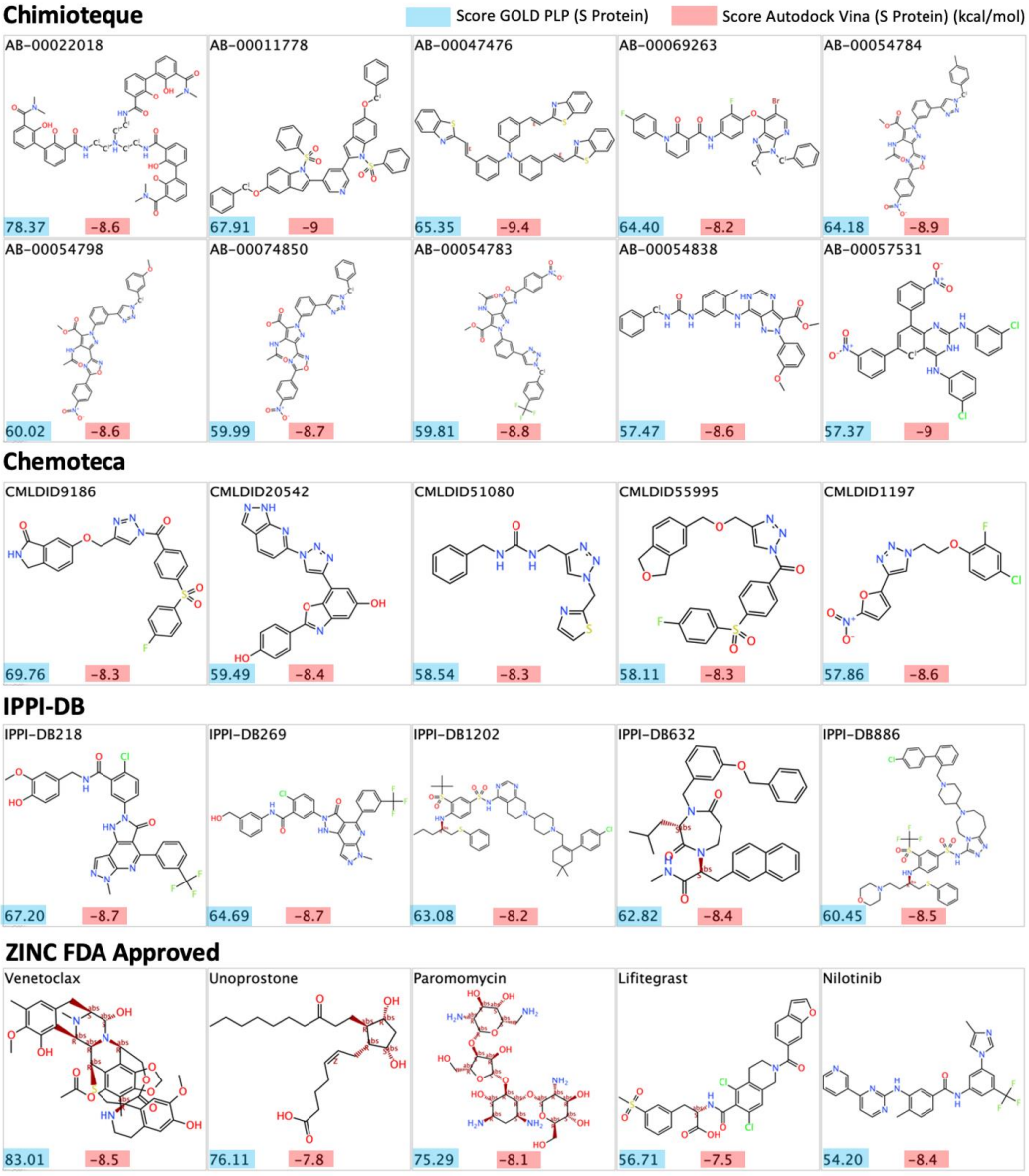
	Chimioteque			Docking Scores					
Ranking	Reference	PLP Score, S Protein	PLP Score, Complex	Vina Score, S Protein	Vina Score, Complex	Database	Total Molweight	cLogP	cLogS
1	AB-00022018	78.37	73.90	-8.6	-8.3	Chimioteque	945.687	4.6851	-6.929
2	AB-00011778	67.91	68.38	-9.0	-8.5	Chimioteque	766.664	7.4365	-15.107
3	AB-00047476	65.35	78.98	-9.4	-10.8	Chimioteque	692.721	10.897	-12.992
4	AB-00069263	64.40	52.45	-8.2	-8.4	Chimioteque	633.303	5.5531	-7.944
5a	AB-00054784	64.18	65.73	-8.9	-8.9	Chimioteque	595.406	2.4006	-7.442
5b	AB-00054798	60.02	55.92	-8.6	-8.9	Chimioteque	611.405	1.9867	-7.116
5c	AB-00074850	59.99	61.34	-8.7	-8.9	Chimioteque	571.384	1.6288	-6.97
5d	AB-00054783	59.81	65.04	-8.8	-9.2	Chimioteque	652.400	2.905	-7.876
6	AB-00054838	57.47	50.47	-8.6	-8.8	Chimioteque	514.396	2.4105	-7.519
7	AB-00057531	57.37	56.76	-9.0	-9.2	Chimioteque	606.320	5.7237	-10.631

	Chemoteca			Docking Scores					
Ranking	Reference	PLP Score, S Protein	PLP Score, Complex	Vina Score, S Protein	Vina Score, Complex	Database	Total Molweight	cLogP	cLogS
1	CMLDID9186	69.76	68.59	-8.3	-8.5	Chemoteca	492.486	2.2402	-6.321
2	CMLDID20542	59.49	62.84	-8.4	-8.2	Chemoteca	411.380	3.1201	-4.755
3	CMLDID51080	58.54	70.13	-8.3	-8.8	Chemoteca	328.399	0.1693	-1.876
4	CMLDID55995	58.11	58.15	-8.3	-8.4	Chemoteca	493.514	2.1139	-6.322
5	CMLDID1197	57.86	60.47	-8.6	-8.4	Chemoteca	352.708	1.7547	-4.49

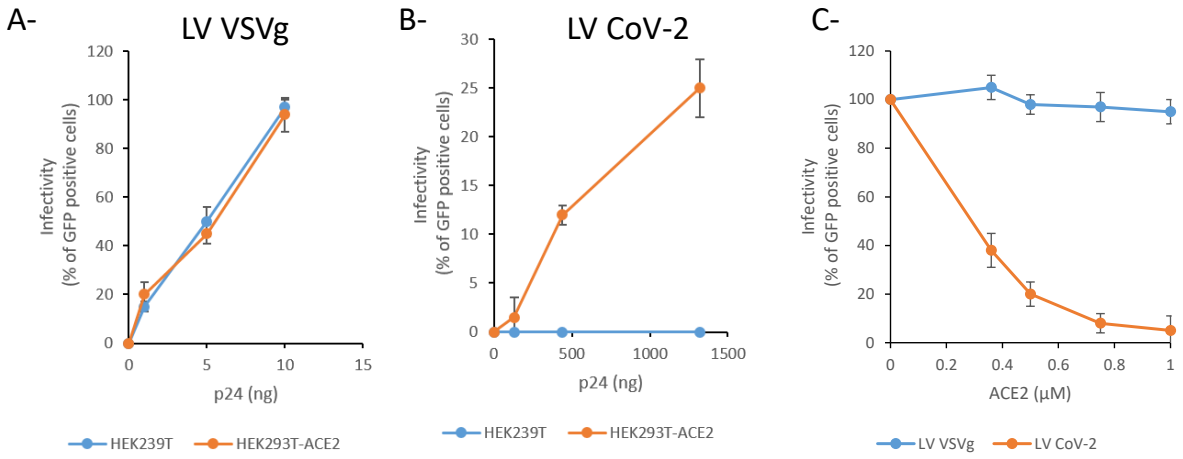
	IPPI-DB			Docking Scores					
Ranking	Reference	PLP Score, S Protein	PLP Score, Complex	Vina Score, S Protein	Vina Score, Complex	Database	Total Molweight	cLogP	cLogS
1	IPPI-DB218	67.20	65.00	-8.7	-9.2	IPPI-DB	622.990	4.5836	-7.022
2	IPPI-DB269	64.69	50.62	-8.7	-9.5	IPPI-DB	592.964	4.6926	-7.368
3	IPPI-DB1202	63.08	60.73	-8.2	-6.8	IPPI-DB	919.717	8.3977	-9.953
4	IPPI-DB632	62.82	59.56	-8.4	-6.3	IPPI-DB	591.750	5.4497	-6.238
5	IPPI-DB886	60.45	69.70	-8.5	-8.1	IPPI-DB	987.631	7.3494	-8.382

	ZINC FDA Approved			Docking Scores					
Name	Reference	PLP Score, S Protein	PLP Score, Complex	Vina Score, S Protein	Vina Score, Complex	Database	Total Molweight	cLogP	cLogS
Venetoclax	ZINC000150338755	83.01	66.81	-8.5	-9.5	FDA Approved Zinc	761.846	4.527	-5.064
Unoprostone	ZINC000008214703	76.11	62.50	-7.8	-7.1	FDA Approved Zinc	382.539	4.7789	-4.351
Paromomycin	ZINC000060183170	75.29	55.54	-8.1	-7.7	FDA Approved Zinc	615.631	-9.1987	0.236
Lifitegrast	ZINC000084668739	56.71	51.57	-7.5	-8.4	FDA Approved Zinc	615.489	3.9144	-7.272
Nilotinib	ZINC000006716957	54.20	56.04	-8.4	-8.6	FDA Approved Zinc	529.525	5.1058	-8.55

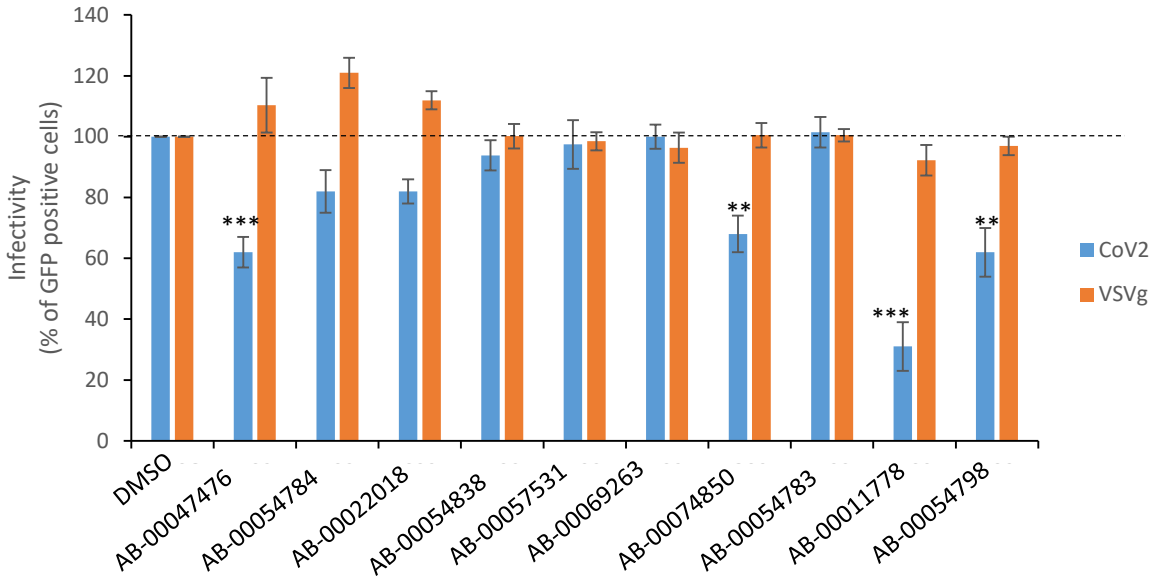
S1. Best selected compounds from the virtual screening. 100 ns molecular dynamics simulation was used with AMBER force field and TIP3P water box on the published S/ACE1 complex. The MuTaLig Virtual Chemotheca (ca. 60,000 molecules, http://chemotheca.unicz.it), the ZINC FDA Approved and ZINC In-trials Database (1379 and 5811 molecules for evaluation for Drug Repurposing, https://zinc.docking.org), The French National chemical library (Chimiothèque Nationale) (70,000 molecules, https://chembiofrance.cn.cnrs.fr/fr/), and the Inhibitors of Protein-Protein Interactions Database (1,956 molecules, https://ippidb.pasteur.fr/) were used for the screen. The best compounds from each library were then sorted and reported here.



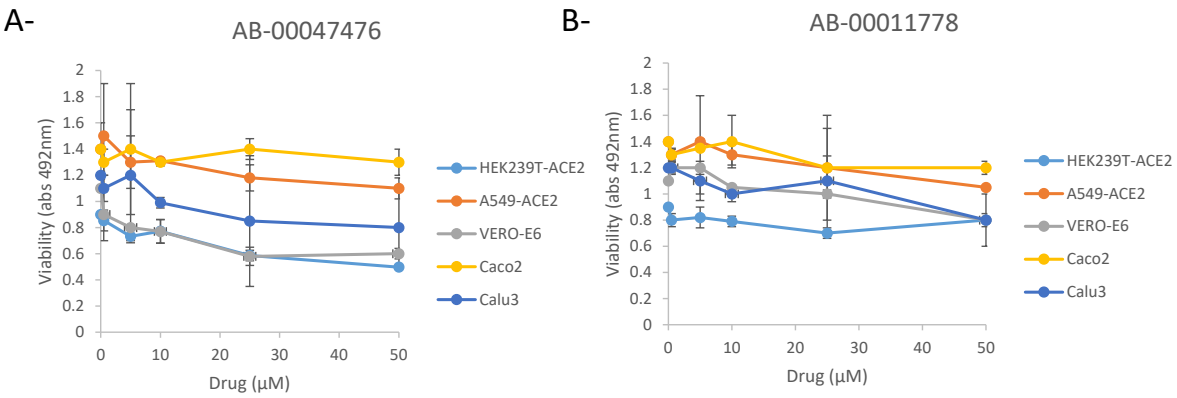
S2. Structure of the best selected compounds. The VINA and PLP scores were also reported in the figure. The compounds are listed with two different scoring functions and their calculated molecular parameters. Charts with VINA scores (the more negative the better) and PLP scores (the higher the better) are shown



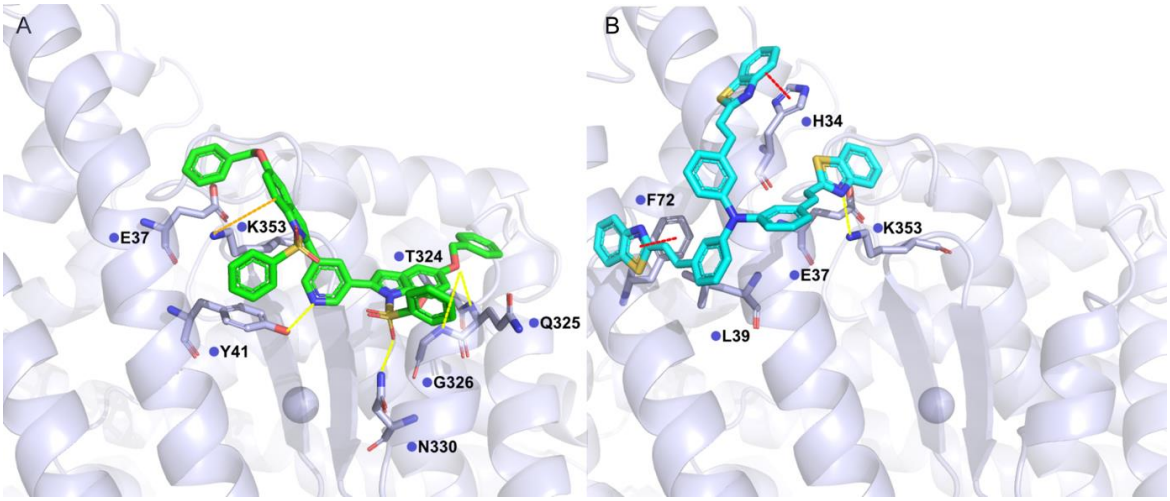
S3. Infectivity of the lentiviruses pseudotyped with the SARS-CoV-2 S protein (LV CoV-2) or the VSVg glycoprotein (LV VSVg) in HEK293T and HEK293T-ACE2 cells. LV VSVg (**A**) and LV CoV-2 (**B**) have been used for transducing HEK293T or HEK293T-Ace2 cells with increasing MOI reported as ng of p24. The infectivity was measured the percentage of GFP positive cells by flow cytometry. Increasing concentrations of soluble ACE2 protein have been added to the CoV-2 or VSVg LVs before transduction (**C**). Data are shown as means of at least three independent experiments ± standard deviation (SD).



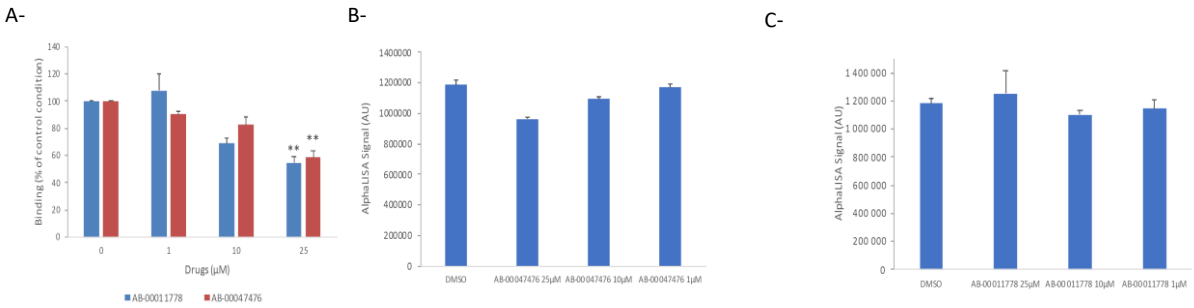
S4. Screening of CN drugs inhibiting SARS-CoV-2 entry using a lentiviral pseudovirus system. Drugs were tested for their infectivity of both VSVg and SARS-CoV-2 S pseudotyped lentiviruses in HEK293T-ACE2 cells at 10µM AB-00047476 and AB-00011778 were selected for further characterization using increasing concentrations of drug (see **Figure 2**). Data are shown as the means of at least three independent experiments ± the standard deviations. ***p<0.001, **p<0.01 (Student's t-test).



S5. Cytotoxicity of AB-00047476 and AB-00011778 compounds in various cell lines. Cells were seeded at the density of 20,000 cells/well in a 96 well plate containing 100 µL complete DMEM (Gibco, USA) supplemented with 10% FBS (Gibco, USA) and 1% Penstrep (Gibco, USA). Cells were incubated for 12 hours at 37º C in humidified 5% CO2 incubator for adherence. After 12-hour incubation, the media was replaced with fresh media, and cells were treated with compounds. Untreated cells were considered as negative control, DMSO treated cells were considered as the vehicles. After the treatment, cells were incubated at 37 º C in humidified 5% CO2 incubator. 48-hour post-treatment, 20 µL of MTT substrate (5 mg/mL) was added in each well and incubated for 4 additional hours at 37º C in the dark. The media was then carefully removed, and 492nm absorbance was measured. The viability of the cells (492nm absorbance in MTT assay) was plotted against the increasing concentration of drugs. Data are shown as means of at three independent experiments. Data are shown as means of five independent experiments ± (SD).



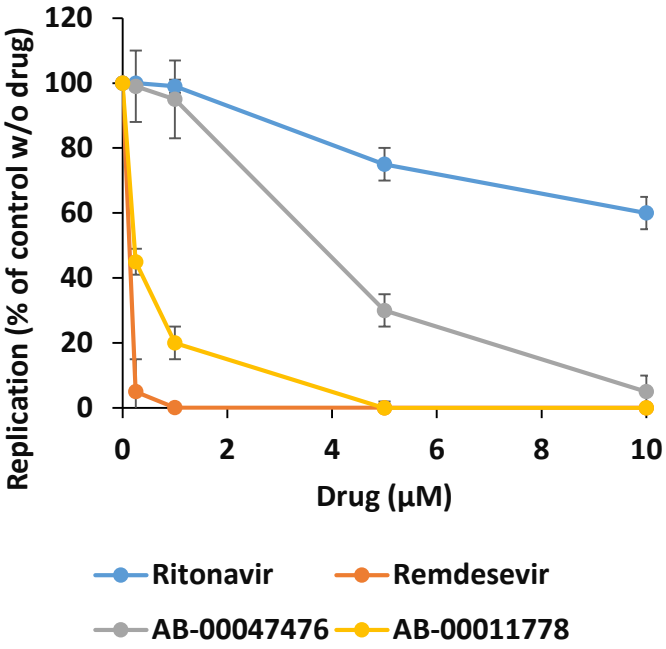
S6. Molecular docking of AB-00011778 and AB-00047476 and ACE2 alone. Data were obtained from the predicted binding poses of the compounds to ACE2 around the interface region. The interacting amino acid residues are highlighted. (A) AB-00011778 bound to ACE2 alone; (B) AB-00047476 bound to ACE2 alone.



S7. Effects of AB-00011778 and AB-00047476 on the *in vitro* S-RBD/ACE2 interaction using AlphaLISA and biolayer interferometry (BLI) technologies. An optimal final concentration of 3nM for each recombinant protein was previously established with cross-titration experiments. Proteins were diluted in the binding buffer (phosphate-buffered saline (PBS) pH 7.4, 0.1% (w/v) bovine serum albumin). For the AlphaLISA competition assay, increasing concentrations of AB-00011778 and AB-00047476 drugs (1 to 25 µM, 1% DMSO final concentration) were preincubated with S-RBD(His)$_6$ for 30 min before being mixed with ACE2-Biot for 2h with rotation at room temperature. Next, 5µL of anti-6X His acceptor beads (Perkin Elmer, reference AL178) were added and after 1h of incubation at RT with rotation, 5 µL of streptavidin donor acceptor beads (Perkin Elmer, reference 6760002) were also mixed to the wells. This established a final concentration of 20 µg/mL for each bead. The plate was then incubated for 1h at RT in the dark before the AlphaLISA signal was detected using an EnSpire Multimode Plate Reader (Perkin Elmer). Negative control with binding buffer was used to control the assay quality. For the competition assay (**A**), increasing concentrations (1 to 25 µM) of AB-00011778 and AB-00047476 were preincubated with S-RBD(His)$_6$ in the plate before being mixed with ACE2-Biot for 2 h. Anti-6XHis acceptor and streptavidin donor beads were used for complex capture after 2 h of incubation with the two partners. Increasing concentrations of AB-00011778 and AB-00047476 were incubated for 30 min with S-RBD(His)$_6$ before being mixed with ACE2-Biot for 2 h. The microplate results were read after 2 h of incubation with the anti-6X His acceptor and streptavidin donor beads. AB-00047476 (**B**) and AB-00011778 (**C**) have been then tested for their propriety to interfere with the AlphaLISA interaction signal using the Truehits counterscreen kit following the manufacturer conditions (PerkinElmer). Data are shown as means of at least three independent experiments ± (SD).

Mutant	Common Name	Pango Name	Mutations in the S-RDB
Alpha	UK	B.1.1.7	N501Y
Beta	South Africa	B.1.351	K417N, E484K, N501Y
Gamma	Brazil	B.1.1.28.1	K417T, E484K, N501Y
Delta	India	B.1.617.2	L452R, T478K
Omicron	-	B.1.1.529	G339D, S371L, S373P, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493R, G496S, Q498R, N501Y, Y505H

S8. Description of the SARS-CoV-2 mutants modelled in the evaluation of the S-RDB/ACE2 interaction



S9. Comparison of the effects of Remdesivir, Ritonavir, AB-00011778 and AB-00047476 on SARS-CoV-2 replication in human pulmonary cells. A549-ACE2 were incubated with the SARS-CoV-2 reference strain (MOI=1) and increasing concentrations of the tested compounds. Replication was evaluated by quantifying the viral genome copies after 24 hours. Data are reported as the means from two independent experiments and are expressed as a percentage of the control without molecule ± the standard deviations.