

APPENDIX

for

A systems-level study reveals host-targeted repurposable drugs against SARS-CoV-2 infection

~~Systems-level analysis reveals anti-SARS-CoV-2 repurposable drugs and compounds targeting the host cell~~

Fangyuan Chen^{†,1,2}, Qingya Shi^{†,1,2}, Fen Pei^{†,1,3}, Andreas Vogt^{†,1,3}, Rebecca A. Porritt^{4,8}, Gustavo Garcia Jr⁵, Angela C. Gomez⁴, Mary H. Cheng¹, Mark Schurdak^{1,3}, Bing Liu¹, Stephen Y. Chan^{6,7}, Vaithilingaraja Arumugaswami⁵, Andrew M Stern^{1,3}, D Lansing Taylor^{1,3}, Moshe Arditi^{4,8}, and Ivet Bahar^{*,1,3}

¹Department of Computational and Systems Biology, School of Medicine, University of Pittsburgh, Pittsburgh, PA, 15213, USA; ²School of Medicine, Tsinghua University, Beijing, 100084, China; ³University of Pittsburgh Drug Discovery Institute, Pittsburgh, PA 15213; ⁴Department of Pediatrics, Division of Pediatric Infectious Diseases and Immunology, Cedars-Sinai Medical Center, Los Angeles, CA, 90048; ⁵Department of Molecular and Medical Pharmacology, David Geffen School of Medicine, University of California and Eli and Edythe Broad Center of Regenerative Medicine and Stem Cell Research, University of California, Los Angeles; ⁶Pittsburgh Heart, Lung, Blood, and Vascular Medicine Institute, and ⁷Division of Cardiology, Department of Medicine, University of Pittsburgh Medical Center, Pittsburgh, PA, 15217; ⁸Biomedical Sciences, Infectious and Immunologic Diseases Research Center, Cedars-Sinai Medical Center, Los Angeles, CA, 90048

[†] These authors made equal contribution

* **Correspondence:** Dr. Ivet Bahar, bahar@pitt.edu

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SUPPLEMENTARY FIGURES

A-C. Identification of DEGs from SARS-CoV-2 infected A-549 cells; determination of antiviral signature

D. Screening the antiviral signature against CMap to identify candidate compounds

E. Identification on compounds whose targets are known or predictable, using **QuartataWeb**

G. Network Proximity analysis using the human lung PPI network to prioritize the compounds closest to disease modules in the SARS-CoV-2-host cell interactome

H I. Interaction-pattern-based clustering based on **QuartataWeb**, and final selection of high priority compounds for experimental testing

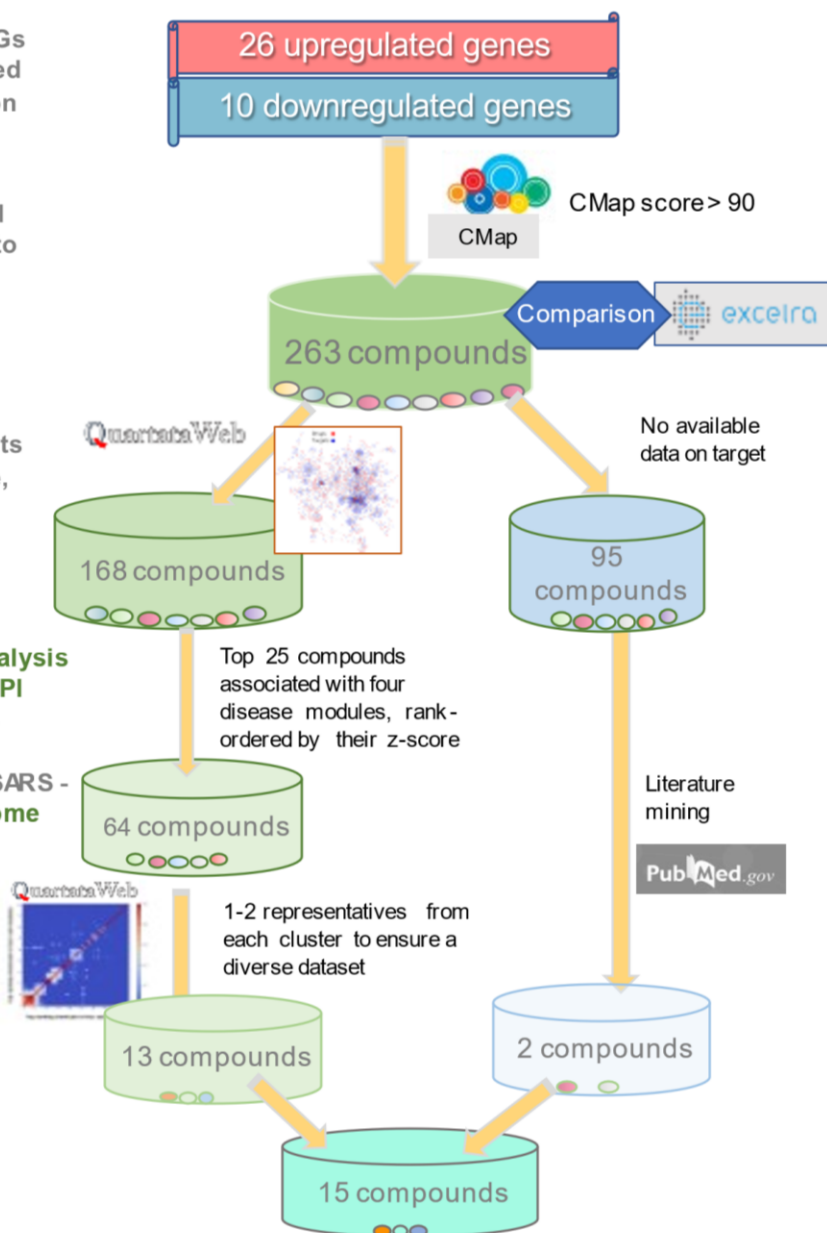


Figure S1. Identification of candidate compounds/drugs, their prioritization and final selection of a small set for experimental tests, illustrated for Dataset 1 (related to Figure 1). The flow diagram depicts the number of compounds/drugs extracted at various stages, indicated by the Steps A-I (on the left) consistent with Figure 1 panels A-I. The original analysis of transcriptomics data from A549 cells leads to 36 DEGs, whose antiviral signature screened against CMap database identifies 263 candidate compounds. Comparison with Excelra DB shows those (10 of them) already listed therein. Of these 263 compounds, 168 have target information available and/or predictable in QuartataWeb (Li et al, 2020) – an interface that utilizes as input DrugBank and STITCH database. Two different paths are then followed, for the respective subsets of 168 and 95 compounds. In the former case, the targets of these 168 compounds are subjected to network proximity analysis with respect to four disease modules in SARS-CoV-2-host interactome, using

BioSNAP human lung PPI network; this analysis yields 64 compounds, which, upon clustering (using QuartataWeb) to select representatives, are reduced to 13 high-priority compounds. The latter set of 95 compounds are manually analyzed to select two compounds, leading to a total set of 15 high priority compounds that have been further investigated in experiments. The diagram depicts the protocol for antiviral compounds. In the case of anti-cytokine compounds, the same schema without step G is adopted.



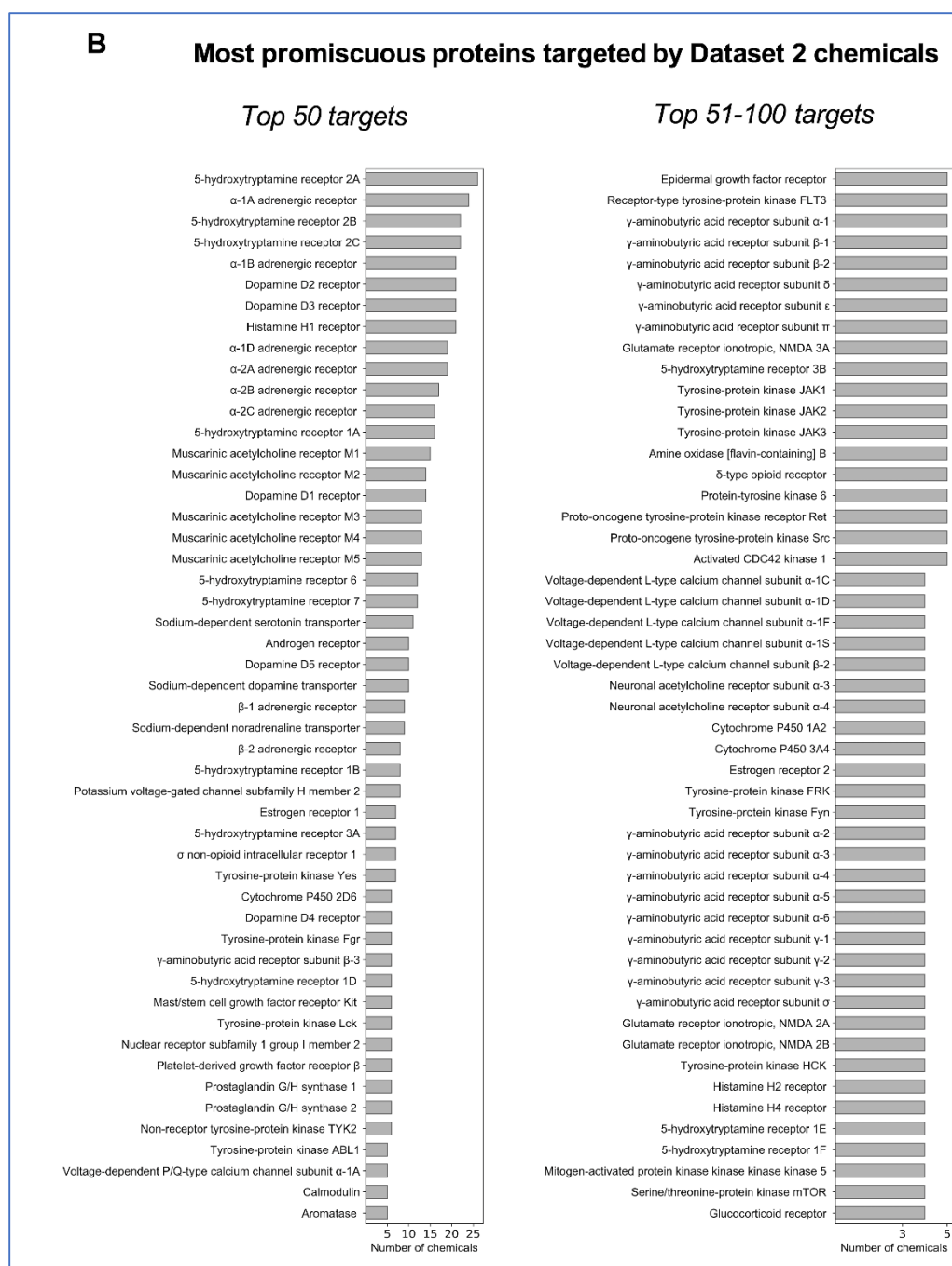


Figure S2. Host cell proteins targeted by potential antiviral (Dataset 1) or anti-cytokine (Dataset 2) compounds/drugs, rank-ordered by their promiscuity, related to Figures 1E and 4. Promiscuity refers to the number of predicted compounds/drugs (also called chemicals) that target the protein. Panel A lists the top 100 targets corresponding to Dataset 1 compounds/drugs. The ordinate lists the proteins, and the horizontal bars (abscissa) show the corresponding number of compounds. Panel B is same as Panel A, for compounds deduced from Dataset 2.

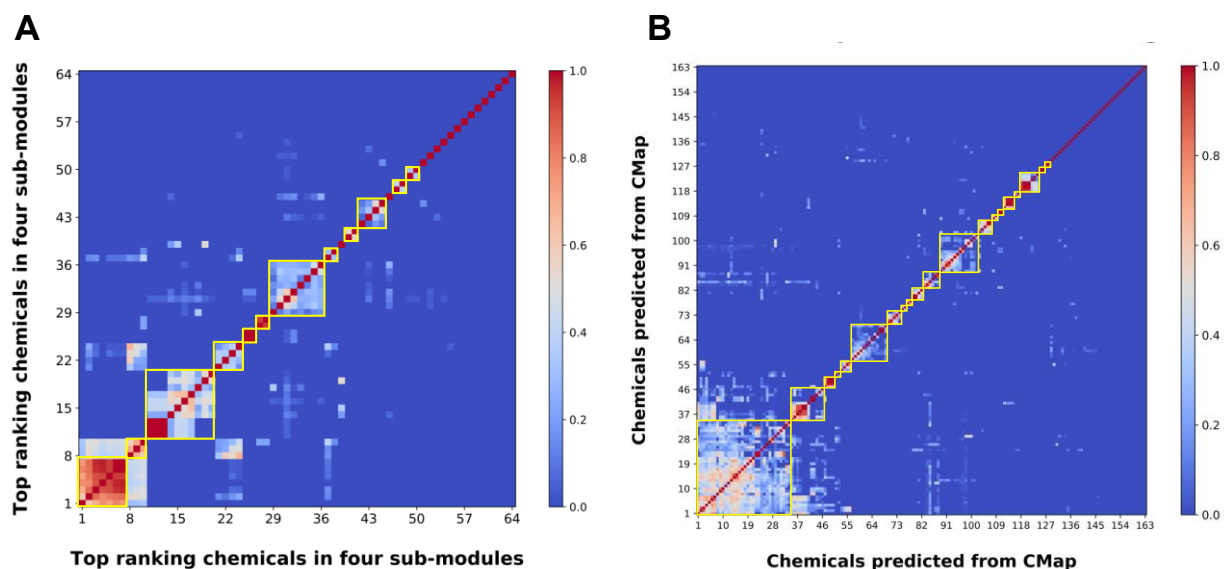


Figure S3. Interaction-pattern-based clustering of top-ranking compounds from four modules and chemicals targeting immune response, related to Figure 1G and H, and Tables 3 and 4. (A) Results for 64 compounds (or chemicals) identified to yield closest proximity to four selected modules. The compounds are clustered based on their interaction patterns with their targets listed in QuartataWeb. 12 main clusters (clusters 1- 8, 10, 11, 13 and 14, from *left to right*, delimited by *yellow squares*) contain two or more compounds each; 16 chemicals do not belong to any cluster. From each of cluster, we selected up to two chemicals based on their side effects and MOA. **(B)** Clustering of 163 chemicals proposed to modulate the immune response, based on anti-cytokine signature gene derived from infected A546-Ace2 cells. The chemicals are clustered based on their interaction patterns reported in DrugBank or STITCH. We distinguish 20 main clusters (marked by *yellow squares*) which contain two or more chemicals, and 35 additional chemicals that do not form clusters.

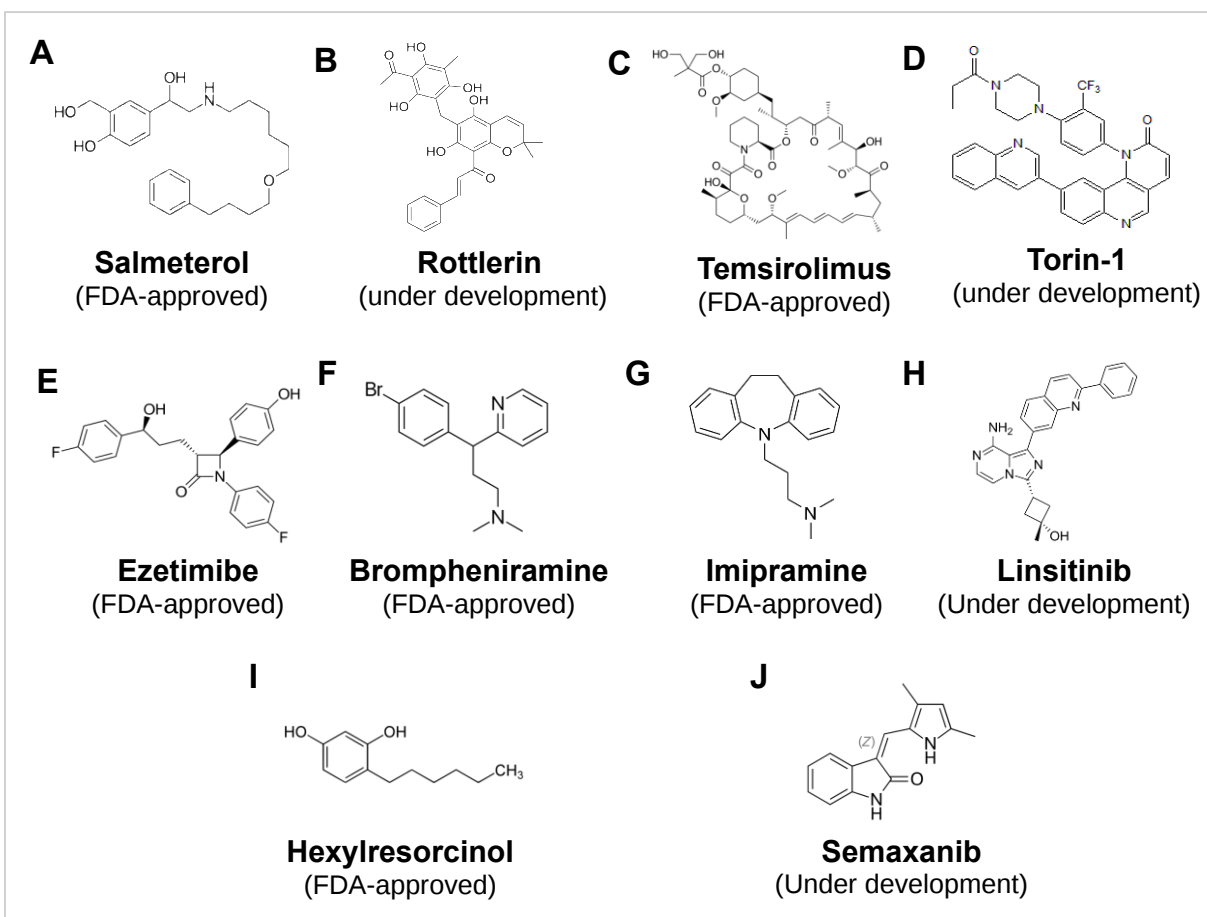


Figure S4. Structure of ten chemicals tested for SARS-CoV-2 infection inhibitory activity *in vitro*, related to Table 3 and Figure 4. Structures of salmeterol, rottlerin, temsirolimus, torin-1, ezetimibe, brompheniramine, imipramine, linsitinib, hexylresorcinol, and semaxanib, selected for *in vitro* assays.

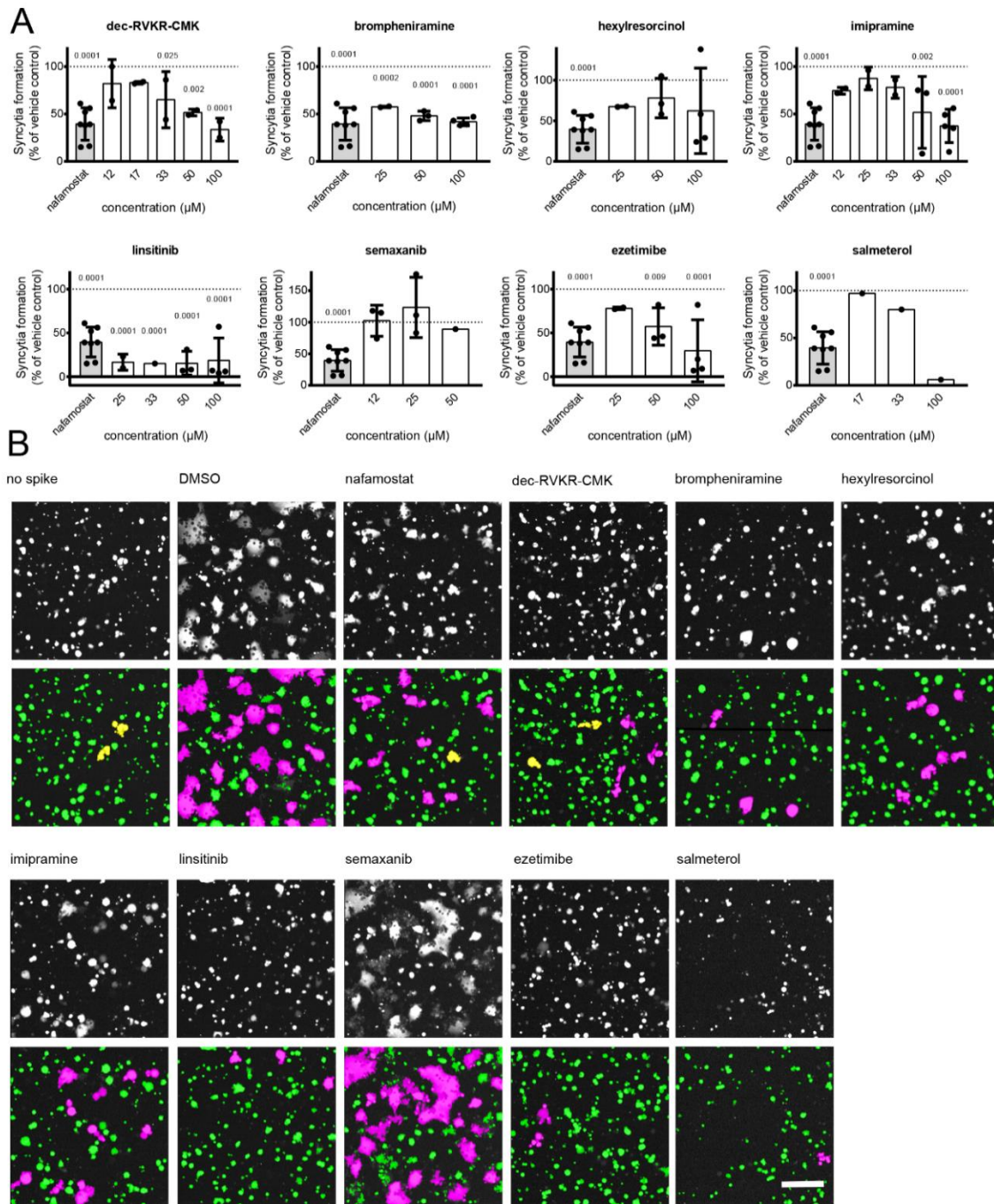


Figure S5. Results from syncytia experiments in HEK293 cells, related to Figure 6. HEK293 acceptor cells transfected with or without ACE2 and TMPRSS2 were seeded in 384 well plates, pretreated with 7-point gradients of test compounds for 1-2 h, and co-cultured for 4 hours with HEK293 donor cells expressing SARS-CoV-2 spike and GFP, or donor cells expressing GFP only (*no spike*). Images of GFP-positive objects were acquired on a confocal high-content imager and analyzed for syncytia formation and total GFP as a measure of cytotoxicity, using a CNT algorithm as described in the Methods Section. A. Quantification of syncytia formation. B. Representative images illustrating syncytia phenotype and compound activity. Images are shown at the 100 μ M condition except nafamostat (5.5 μ M), semaxanib

(50 μ M), and linsitinib (25 μ M). *Upper panels*, raw fluorescence micrographs; *lower panels*, images with CNT overlay. GFP positive objects that met the criteria for syncytia are colored *purple*; cellular aggregates that are not syncytia are shown in *yellow*. Scale bar, 100 μ m. *No spike*, donor cells expressing GFP only. Numbers indicate p-values obtained by one-way ANOVA (non-matched, unpaired) with Dunnett's multiple comparisons test in Graph Pad Prism (v7.00) compared with vehicle control (*dotted line*). No p-value, $p > 0.05$. *Bars and errors* represent the means $\pm$ SD from multiple independent biological repeats, each performed in quadruplicate. No error bars for $n = 1$.

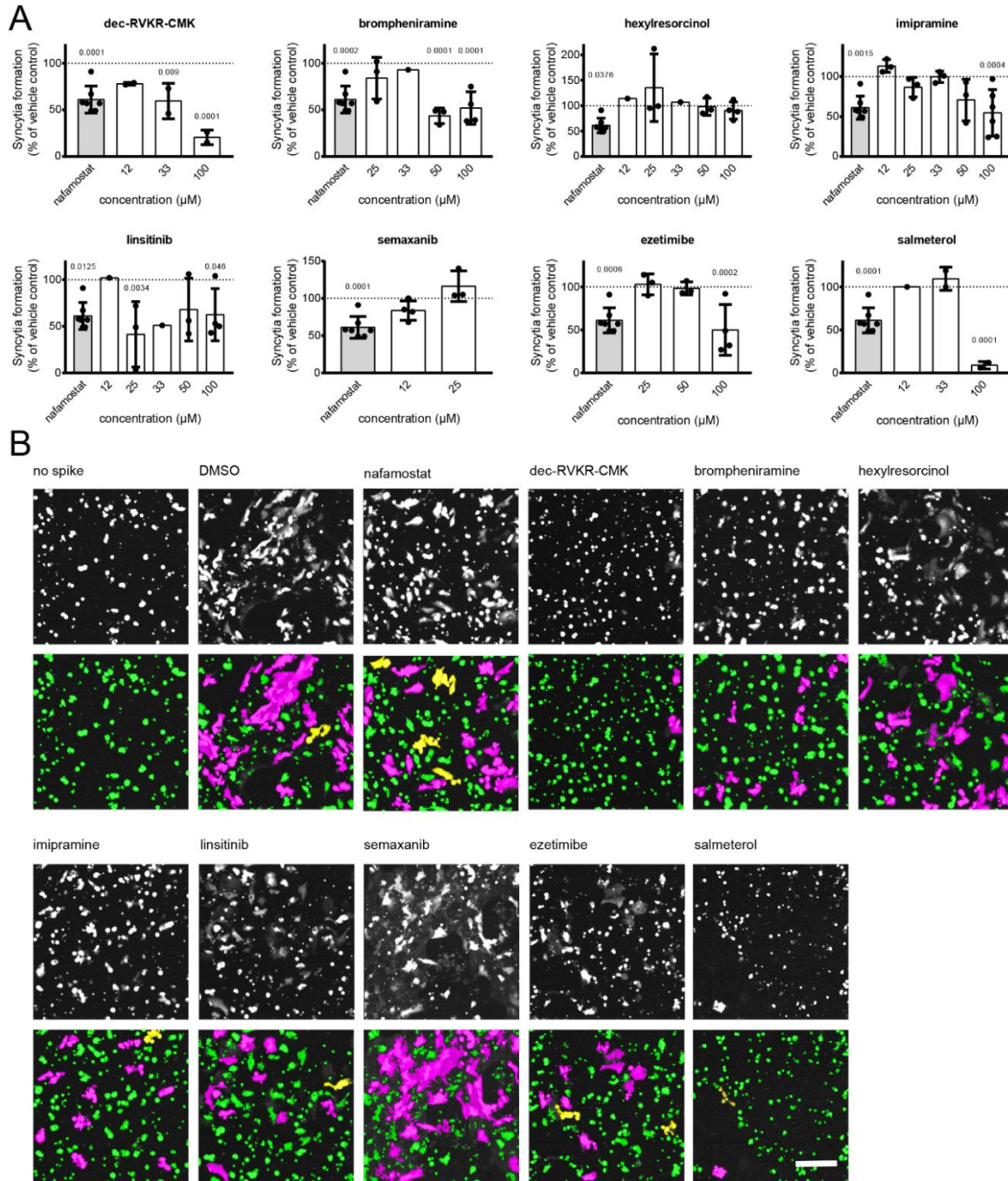


Figure S6. Results from syncytia experiments in Calu-3 cells, related to Figure 6. Calu-3 acceptor cells were seeded in 384 well plates, pretreated with compounds for 1-2 h, and co-cultured for 4 hours with HEK293 donor cells expressing SARS-CoV-2 spike and GFP. Images of GFP-positive objects were acquired on a confocal high-content imager and analyzed for syncytia formation using a CNT algorithm as described in the Methods. **A.** Quantification of syncytia formation. **B.** Representative images illustrating syncytia phenotype and compound activity. Images are shown at the 100 μ M condition except nifamostat (5.5 μ M), semaxanib (50 μ M), and linsitinib (25 μ M). *Upper panels*, raw fluorescence micrographs; *lower panels*, images with CNT overlay. GFP positive objects that met the criteria for syncytia are colored *purple*; cellular aggregates that are not syncytia are shown in *yellow*. **Scale bar**, 100 μ m. *No spike*, donor cells expressing GFP only. Numbers indicate p-values obtained by one-way ANOVA (non-matched, unpaired) with Dunnett's multiple comparisons test in Graph Pad Prism (v7.00) compared with vehicle control (*dotted line*). No p-value, $p > 0.05$. Bars and errors represent the means $\pm$ SD from multiple independent biological repeats, each performed in quadruplicate. No error bars, $n = 1$.

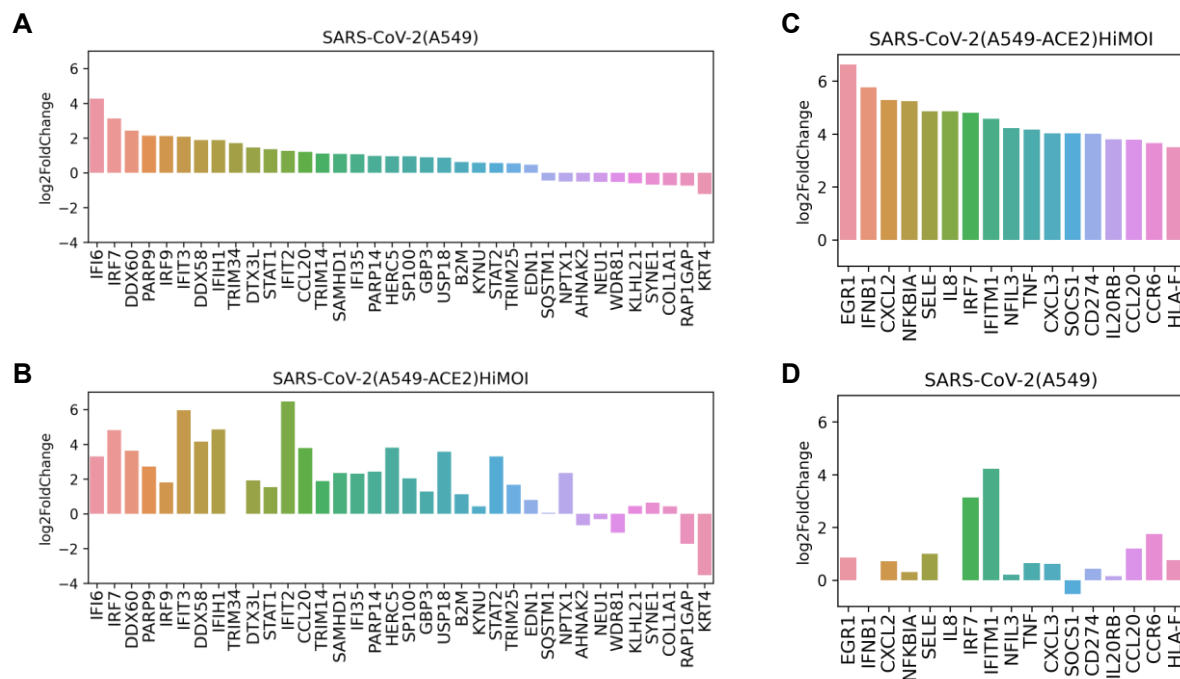


Figure S7. Comparison of the behavior of A546 and A546-ACE2 cells vis-à-vis the expression levels of the genes that have been adopted for defining antiviral and anticytokine signatures. A. The 36 genes of antiviral signature expression in A549 cells (same as Figure 2C). **B.** The 36 genes of antiviral signature expression in A549-ACE2 cells. **C.** The 17 genes of anti-inflammatory signature expression in A549-ACE2 cells (same as Figure 2D). **D.** The 17 genes of anti-inflammatory signature expression in A549 cells.

SUPPLEMENTARY TABLES

Table S1. 120 differentially expressed genes (DEGs) in SARS-CoV-2-infected A549 cells

Gene name	Protein name	log ₂ fold change	P _{adjusted}
Upregulated 100 genes in SARS-CoV-2-infected A549 cells			
MX1	IFN-induced GTP-binding protein Mx1	5.20	1.16E-93
IFI44	IFN-induced protein 44 (Fragment)	4.59	6.80E-04
IFIT1	IFN-induced protein with tetratricopeptide repeats 1 (IFIT-1) (IFN-induced 56 kDa protein) (IFI-56K) (P56)	4.43	6.18E-96
IFI6	IFN α -inducible protein 6	4.27	1.01E-145
OAS2	2'-5'-oligoadenylate synthase 2	4.25	1.49E-06
IFITM1	IFN induced transmembrane protein 1 (9-27), isoform CRA_a	4.22	3.12E-05
ISG15	Ubiquitin-like protein ISG15 (Fragment)	3.80	6.21E-85
IFI27	IFN α -inducible protein 27, mitochondrial (Fragment)	3.54	8.09E-14
IRF7	IFN regulatory factor 7, isoform CRA_a	3.13	5.69E-43
PTPRE	Receptor-type tyrosine-protein phosphatase epsilon (Protein-tyrosine phosphatase epsilon) (R-PTP-epsilon) (EC 3.1.3.48)	3.02	3.36E-10
OASL	2'-5'-oligoadenylate synthase-like protein (Fragment)	2.53	8.17E-07
DDX60	ATP-dependent RNA helicase DDX60	2.42	1.43E-25
CMPK2	Mitochondrial cytidine monophosphate (UMP-CMP) kinase 2 (Fragment)	2.23	7.66E-03
PARP9	Protein mono-ADP-ribosyltransferase PARP9 (Fragment)	2.13	4.32E-43
IRF9	IFN regulatory factor 9	2.11	6.73E-42
IFIT3	IFN-induced protein with tetratricopeptide repeats 3 (IFIT-3) (CIG49) (ISG-60) (IFN-induced 60 kDa protein) (IFI-60K) (Retinoic acid-induced gene G protein) (P60) (RIG-G)	2.07	1.88E-21
SAMD9L	Sterile α motif domain-containing protein 9-like (Fragment)	1.97	5.51E-06
DDX58	Antiviral innate immune response receptor RIG-I	1.88	3.16E-19
IFIH1	IFN-induced helicase C domain-containing protein 1	1.88	4.01E-15
PARP10	Poly [ADP-ribose] polymerase (PARP) (EC 2.4.2.-)	1.83	9.35E-07
SAMD9	Sterile α motif domain-containing protein 9 (Fragment)	1.79	1.76E-07
TRIM34	Tripartite motif-containing protein 34 (IFN-responsive finger protein 1) (RING finger protein 21)	1.71	2.07E-04
HERC6	Probable E3 ubiquitin-protein ligase HERC6	1.52	9.14E-14
REC8	Meiotic recombination protein REC8 homolog (Fragment)	1.51	1.81E-04
OAS1	2'-5' oligoadenylate synthetase 1 p49 isoform (Fragment)	1.51	2.69E-33
DTX3L	E3 ubiquitin-protein ligase DTX3L (EC 2.3.2.27) (B-lymphoma- and BAL-associated protein) (Protein deltex-3-like) (RING-type E3 ubiquitin transferase DTX3L; Rhysin-2)	1.46	1.44E-21
HELZ2	Helicase with zinc finger domain 2 (ATP-dependent helicase PRIC285) (transcriptional coactivator) (PPAR- α -interacting complex protein 285) (PPAR- γ DNA-binding domain-interacting protein 1) (PDIP1) (Peroxisomal proliferator-activated receptor A-interacting complex 285 kDa protein)	1.38	3.78E-17
EIF2AK2	eIF2AK2 protein	1.36	3.59E-12
STAT1	Signal transducer and activator of transcription 1 (Fragment)	1.35	1.90E-28
OAS3	2'-5'-oligoadenylate synthetase 3, 100kDa, isoform CRA_a	1.35	3.29E-26
IFI16	I-IFN-inducible protein 16	1.35	4.30E-03
PLSCR1	Phospholipid scramblase (Fragment)	1.27	4.77E-13
IFIT2	IFN-induced protein with tetratricopeptide repeats 2	1.25	1.68E-02
SP110	Sp110 nuclear body protein (Fragment)	1.23	6.32E-08
CCL20	C-C motif chemokine 20 (Fragment)	1.20	3.03E-06
FGG	Fibrinogen γ chain	1.19	5.53E-03
DDX60L	Putative ATP-dependent RNA helicase DDX60 (EC 3.6.4.13)	1.13	1.68E-05

CFB	Complement factor B (Fragment)	1.12	7.26E-08
TRIM14	Tripartite motif-containing 14, isoform CRA_c	1.09	3.97E-11
IFIT5	IFN-induced protein with tetratricopeptide repeats 5 (IFIT-5) (Retinoic acid- and IFN-inducible 58 kDa protein) (P58)	1.09	3.90E-07
SAMHD1	Deoxynucleoside triphosphate triphosphohydrolase SAMHD1	1.08	5.81E-12
PHF11	PHD finger protein 11 (cDNA FLJ56933, highly similar to Homo sapiens PHD finger protein 11 (PHF11), transcript variant 1, mRNA)	1.07	2.63E-03
IFI35	IFN-induced 35 kDa protein (IFP 35) (Ifi-35)	1.06	1.54E-08
LAP3	Cytosol aminopeptidase (Fragment)	1.03	2.82E-13
CXCL5	C-X-C motif chemokine 5 (ENA-78(1-78)) (Epithelial-derived neutrophil-activating protein 78) (Small-inducible cytokine B5) [Cleaved into: ENA-78(8-78); ENA-78(9-78)]	0.96	3.86E-08
PARP14	Protein mono-ADP-ribosyltransferase PARP14	0.96	4.02E-08
HERC5	E3 ISG15--protein ligase HERC5 (HECT and RLD domain-containing E3 ubiquitin protein ligase 5) (Fragment)	0.94	3.70E-05
SP100	Nuclear autoantigen Sp-100 (Fragment)	0.94	1.23E-07
BCL2A1	Bcl-2-related protein A1 (Bcl-2-like protein 5) (Bcl2-L-5) (Hemopoietic-specific early response protein) (Protein BFL-1) (Protein GRS)	0.93	1.15E-02
IFITM3	IFN-induced transmembrane protein 3	0.91	1.75E-03
GBP3	Guanylate-binding protein 3	0.89	1.26E-02
USP18	Ubl carboxyl-terminal hydrolase 18 (EC 3.4.19.-) (43 kDa ISG15-specific protease) (hUBP43) (ISG15-specific-processing protease) (Ubl thioesterase 18)	0.86	1.21E-04
CP	CP protein (Ceruloplasmin (Ferroxidase)) (Ceruloplasmin (Ferroxidase), isoform CRA_a)	0.86	8.59E-04
CFH	Complement factor H	0.85	1.15E-02
PARP12	Poly (ADP-ribose) polymerase family, member 12, isoform CRA_b (Zinc finger CCCH type domain containing 1)	0.82	9.48E-05
STEAP1	Six transmembrane epithelial antigen of the prostate 1, isoform CRA_a	0.81	9.43E-03
EHF	ETS homologous factor (Fragment)	0.81	1.60E-02
PTGS2	Prostaglandin-endoperoxidase synthase 2 (EC 1.14.99.1) (Fragment)	0.80	1.47E-03
C1R	Complement C1r subcomponent	0.80	4.43E-07
SAT1	Diamine acetyltransferase 1	0.78	1.89E-06
BIVM-ERCC5	BIVM-ERCC5 readthrough (Fragment)	0.76	3.05E-02
C19orf66	Shiftless antiviral inhibitor of ribosomal frameshifting protein (SFL) (SHFL) (IFN-regulated antiviral protein) (IRAV) (Repressor of yield of DENV protein) (RyDEN)	0.76	1.03E-03
SNAP25	Synaptosomal-associated protein 25 (Fragment)	0.76	2.62E-03
CXCL8	Multifunctional fusion protein [Includes: Interleukin-8 (IL-8) (C-X-C motif chemokine 8)]	0.75	1.17E-06
PDK4	Protein-serine/threonine kinase (EC 2.7.11.-)	0.75	1.29E-02
PNPT1	Polyribonucleotide nucleotidyltransferase 1, mitochondrial	0.74	9.53E-04
MMD	Monocyte to macrophage differentiation factor	0.72	2.08E-02
APOL6	Apolipoprotein L, 6 (Apolipoprotein L6) (cDNA FLJ38562 fis, clone HCHON2004002, similar to Apolipoprotein-L6)	0.71	3.42E-02
C1S	Complement C1s subcomponent	0.71	1.43E-06
CXCL2	C-X-C motif chemokine	0.71	2.37E-04
UBE2L6	Ubiquitin/ISG15-conjugating enzyme E2 L6 (Fragment)	0.71	3.07E-04
NUCB2	Nesfatin 1 (Fragment)	0.70	3.56E-02
APOL1	Apolipoprotein L, 1, isoform CRA_b	0.70	5.96E-03
PLA2G4A	Cytosolic phospholipase A2 (cPLA2) (Phospholipase A2 group IVA)	0.70	1.93E-02
PAPPA-AS1	Protein PAPPAS (DIPLA1 antisense RNA 1)	0.69	2.25E-02
TYMP	Thymidine phosphorylase isoform 2	0.66	1.33E-02
FGA	Fibrinogen α chain	0.66	9.95E-04

PTPN12	Tyrosine-protein phosphatase non-receptor type 12	0.66	1.56E-02
FILIP1	Filamin A interacting protein 1, isoform CRA_c (Filamin-A-interacting protein 1)	0.66	2.08E-02
ESF1	ESF1 homolog	0.64	3.36E-02
NCOA7	Nuclear receptor coactivator 7, isoform CRA_c	0.63	2.58E-03
CXCL3	C-X-C motif chemokine 3 (GRO- γ (1-73)) (Growth-regulated protein γ) (GRO- γ) (Macrophage inflammatory protein 2- β) (MIP2- β) [Cleaved into: GRO- γ (5-73)]	0.62	1.61E-02
B2M	B-2-microglobulin	0.61	1.17E-02
TDRD7	Tudor domain-containing protein 7 (PCTAIRE2-binding protein) (Tudor repeat associator with PCTAIRE-2) (Trap)	0.61	3.92E-03
C3	Complement C3 (Fragment)	0.61	1.47E-03
PSIP1	Alternative protein PSIP1	0.60	5.96E-03
KTN1	Kinectin 1 (Kinesin receptor), isoform CRA_a (Kinectin 1 (Kinesin receptor), isoform CRA_b)	0.59	3.36E-02
CXCL1	Growth-regulated α protein (C-X-C motif chemokine 1) (GRO- α (1-73)) (Melanoma growth stimulatory activity) (MGSA) (Neutrophil-activating protein 3) (NAP-3) [Cleaved into: GRO- α (4-73); GRO- α (5-73); GRO- α (6-73)]	0.59	2.00E-03
TCIM	Transcriptional and immune response regulator (Thyroid cancer protein 1) (TC-1)	0.58	5.53E-03
ADAR	Double-stranded RNA-specific adenosine deaminase (fragment)	0.57	1.92E-05
DKK1	Dickkopf-like protein 1	0.57	1.24E-03
KYNU	Kynureninase (Fragment)	0.57	2.98E-02
AREG	Amphiregulin	0.57	2.09E-03
LGALS3BP	Lectin galactoside-binding soluble 3 binding protein isoform 1 (CRA_d) (Fragment)	0.55	1.25E-02
CDH1	Cadherin-1	0.55	2.88E-03
STAT2	Signal transducer and activator of transcription 2	0.55	7.66E-03
HIF1A	Hypoxia-inducible factor 1, α subunit (Basic helix-loop-helix transcription factor), isoform CRA_a	0.54	3.82E-02
TRIM25	E3 ubiquitin/ISG15 ligase TRIM25	0.53	7.01E-04
HSP90B1	Endoplasmin	0.48	3.44E-02
EDN1	Endothelin-1 (Preproendothelin-1) (PPET1) [Cleaved into: Endothelin-1 (ET-1); Big endothelin-1]	0.45	2.50E-02
Downregulated 20 genes in SARS-CoV-2-infected A549 cells			
SQSTM1	Sequestosome-1	-0.46	2.50E-02
NPTX1	Neuronal pentraxin-1 (NP1) (Neuronal pentraxin I) (NP-I)	-0.51	2.25E-02
AHNAK2	Protein AHNAK2	-0.51	3.19E-03
NEU1	Sialidase-1	-0.52	1.24E-02
WDR81	WD repeat-containing protein 81	-0.53	2.50E-02
FAM102A	Protein FAM102A (Early estrogen-induced gene 1 protein)	-0.57	2.34E-03
DANCR	Uncharacterized protein DANCR (Anti-differentiation ncRNA protein) (Small nucleolar RNA host gene protein 13)	-0.59	1.84E-02
NT5DC2	5'-nucleotidase domain-containing protein 2 (Fragment)	-0.59	1.23E-02
MAP3K14	Mitogen-activated protein kinase kinase kinase 14 (Fragment)	-0.59	1.44E-02
KLHL21	Kelch-like protein 21	-0.61	5.58E-03
LOC284454	/ (ncRNA)	-0.64	3.92E-02
SYNE1	Nesprin-1	-0.68	2.34E-03
COL1A1	Collagen, type I, α 1, isoform CRA_a	-0.73	1.05E-03
OSGIN1	Oxidative stress-induced growth inhibitor 1 (Fragment)	-0.74	6.80E-04
RAP1GAP	Rap1 GTPase-activating protein 1	-0.74	6.04E-05
NPIP5	Nuclear pore complex-interacting protein family member B5	-0.83	1.06E-02
UAP1L1	UDP-N-acetylhexosamine pyrophosphorylase-like protein 1	-0.84	4.55E-04
NUPR1	Nuclear protein 1	-0.99	5.96E-03
NECAB2	N-terminal EF-hand calcium-binding protein 2 (Fragment)	-1.12	2.50E-02
KRT4	Keratin, type II cytoskeletal 4	-1.23	1.84E-04

Table S2A. Properties of the 36 DEGs that define the antiviral gene signature derived from the transcriptome of SARS-CoV-2-infected A549 cells

Index	Gene name	Protein name	Log ₂ f Change	Database	GO Annotation	GO number
UPREGULATED GENES THAT SHOULD BE UPREGULATED BY SMALL MOLECULES						
1	IFI6	IFN α -inducible protein 6	4.27	GO:BP	type I IFN signaling pathway	GO:0060337
					defense response to virus	GO:0051607
					cellular response to type I IFN	GO:0071357
					response to type I IFN	GO:0034340
2	IRF7	IFN regulatory factor 7, isoform CRA_a	3.13	GO:BP	cellular response to IFN- γ	GO:0071346
					type I IFN signaling pathway	GO:0060337
					cellular response to type I IFN	GO:0071357
					response to type I IFN	GO:0034340
					response to IFN- γ	GO:0034341
					defense response to virus	GO:0051607
					regulation of response to cytokine stimulus	GO:0060759
3	DDX60	ATP-dependent RNA helicase DDX60	2.42	GO:BP	IFN- γ -mediated signaling pathway	GO:0060333
					defense response to virus	GO:0051607
4	PARP9	Protein mono-ADP-ribosyltransferase PARP9 (Fragment)	2.13	GO:BP	regulation of response to cytokine stimulus	GO:0060759
					cellular response to IFN- γ	GO:0071346
					IFN- γ -mediated signaling pathway	GO:0060333
					response to IFN- γ	GO:0034341
5	IRF9	IFN regulatory factor 9	2.11	GO:BP	defense response to virus	GO:0051607
					response to type I IFN	GO:0034340
					cellular response to IFN- γ	GO:0071346
					response to IFN- γ	GO:0034341
					IFN- γ -mediated signaling pathway	GO:0060333
					cellular response to type I IFN	GO:0071357
					type I IFN signaling pathway	GO:0060337
6	IFIT3	IFN-induced protein with tetratricopeptide repeats 3	2.07	GO:BP	defense response to virus	GO:0051607
					cellular response to type I IFN	GO:0071357
					type I IFN signaling pathway	GO:0060337
					response to type I IFN	GO:0034340
7	DDX58	Antiviral innate immune response receptor RIG-I	1.88	GO:BP	defense response to virus	GO:0051607
					regulation of response to cytokine stimulus	GO:0060759
8	IFIH1	IFN-induced helicase C domain-containing protein 1	1.88	GO:BP	defense response to virus	GO:0051607
					regulation of response to cytokine stimulus	GO:0060759
9	TRIM34	Tripartite motif-containing protein 34 (IFN-responsive finger protein 1) (RING finger protein 21)	1.71	GO:BP	defense response to virus	GO:0051607
					response to IFN- γ	GO:0034341
					IFN- γ -mediated signaling pathway	GO:0060333
					cellular response to IFN- γ	GO:0071346
10	DTX3L	E3 ubiquitin-protein ligase DTX3L	1.46	GO:BP	defense response to virus	GO:0051607
11	STAT1	Signal transducer and activator of transcription 1 (Fragment)	1.35	GO:BP	regulation of response to cytokine stimulus	GO:0060759
					type I IFN signaling pathway	GO:0060337
					defense response to virus	GO:0051607
					cellular response to type I IFN	GO:0071357
					negative regulation of viral process	GO:0048525

					response to type I IFN	GO:0034340
					IFN- γ -mediated signaling pathway	GO:0060333
					response to IFN- γ	GO:0034341
					regulation of symbiosis, encompassing mutualism through parasitism	GO:0043903
					negative regulation of multi-organism process	GO:0043901
					cellular response to IFN- γ	GO:0071346
					regulation of viral process	GO:0050792
12	IFIT2	IFN-induced protein with tetratricopeptide repeats 2	1.25	GO:BP	cellular response to type I IFN	GO:0071357
					defense response to virus	GO:0051607
					type I IFN signaling pathway	GO:0060337
					response to type I IFN	GO:0034340
13	CCL20	C-C motif chemokine 20 (Fragment)	1.2	GO:BP	response to IFN- γ	GO:0034341
					cellular response to IFN- γ	GO:0071346
14	TRIM14	Tripartite motif-containing 14, isoform CRA_c	1.09	GO:BP	regulation of viral process	GO:0050792
					regulation of symbiosis, encompassing mutualism through parasitism	GO:0043903
					negative regulation of multi-organism process	GO:0043901
					negative regulation of viral process	GO:0048525
15	SAMHD1	Deoxynucleoside triphosphate triphosphohydrolase SAMHD1	1.08	GO:BP	cellular response to type I IFN	GO:0071357
					negative regulation of multi-organism process	GO:0043901
					regulation of response to cytokine stimulus	GO:0060759
					response to type I IFN	GO:0034340
					defense response to virus	GO:0051607
					type I IFN signaling pathway	GO:0060337
16	IFI35	IFN-induced 35 kDa protein (IFP 35) (Ifi-35)	1.06	GO:BP	type I IFN signaling pathway	GO:0060337
					cellular response to type I IFN	GO:0071357
					response to type I IFN	GO:0034340
17	PARP14	Protein mono-ADP-ribosyltransferase PARP14	0.96	GO:BP	regulation of response to cytokine stimulus	GO:0060759
					IFN- γ -mediated signaling pathway	GO:0060333
					cellular response to IFN- γ	GO:0071346
					response to IFN- γ	GO:0034341
					negative regulation of multi-organism process	GO:0043901
18	HERC5	E3 ISG15--protein ligase HERC5 (Fragment)	0.94	GO:BP	defense response to virus	GO:0051607
19	SP100	Nuclear autoantigen Sp-100 (Fragment)	0.94	GO:BP	cellular response to type I IFN	GO:0071357
					type I IFN signaling pathway	GO:0060337
					response to type I IFN	GO:0034340
					response to IFN- γ	GO:0034341
					IFN- γ -mediated signaling pathway	GO:0060333
20	GBP3	Guanylate-binding protein 3	0.89	GO:BP	cellular response to IFN- γ	GO:0071346
					response to IFN- γ	GO:0034341
					defense response to virus	GO:0051607
					type I IFN signaling pathway	GO:0060337
21	USP18	Ubl carboxyl-terminal hydrolase 18	0.86	GO:BP	cellular response to type I IFN	GO:0071357
					response to type I IFN	GO:0034340
					regulation of response to cytokine stimulus	GO:0060759
					response to IFN- γ	GO:0034341
22	B2M	B-2-microglobulin	0.61	GO:BP	cellular response to IFN- γ	GO:0071346
					IFN- γ -mediated signaling pathway	GO:0060333
23	KYNU	Kynureninase (Fragment)	0.57	GO:BP	response to IFN- γ	GO:0034341
24	STAT2	Signal transducer and activator of transcription 2	0.55	GO:BP	defense response to virus	GO:0051607
					response to type I IFN	GO:0034340
					cellular response to type I IFN	GO:0071357

					type I IFN signaling pathway	GO:0060337
25	TRIM25	E3 ubiquitin/ISG15 ligase TRIM25	0.53	GO:BP	cellular response to IFN- γ	GO:0071346
					regulation of viral life cycle	GO:1903900
					response to IFN- γ	GO:0034341
					negative regulation of viral life cycle	GO:1903901
					IFN- γ -mediated signaling pathway	GO:0060333
					regulation of viral process	GO:0050792
					negative regulation of multi-organism process	GO:0043901
					defense response to virus	GO:0051607
					negative regulation of viral process	GO:0048525
					regulation of symbiosis, encompassing mutualism through parasitism	GO:0043903
26	EDN1	Endothelin-1 (Preproendothelin-1) (PPET1)	0.45	GO:BP	regulation of response to cytokine stimulus	GO:0060759
					response to IFN- γ	GO:0034341
					cellular response to IFN- γ	GO:0071346
DOWREGULATED GENES THAT SHOULD BE UPREGULATED BY SMALL MOLECULES						
1	SQSTM1	Sequestosome-1	-0.46	GO:CC	supramolecular complex	GO:0099080
					intracellular vesicle	GO:0097708
					supramolecular fiber	GO:0099512
					supramolecular polymer	GO:0099081
					cytoplasmic vesicle	GO:0031410
					myofibril	GO:0030016
					sarcomere	GO:0030017
					contractile fiber	GO:0043292
					amphisome	GO:0044753
					P-body	GO:0000932
					autophagosome	GO:0005776
					vesicle	GO:0031982
2	AHNAK2	Protein AHNAK2	-0.51	GO:CC	supramolecular complex	GO:0099080
					intracellular vesicle	GO:0097708
					cytoplasmic vesicle	GO:0031410
					sarcomere	GO:0030017
					supramolecular polymer	GO:0099081
					supramolecular fiber	GO:0099512
					myofibril	GO:0030016
					contractile fiber	GO:0043292
3	NPTX1	Neuronal pentraxin-1 (NP1) (Neuronal pentraxin I) (NP-I)	-0.51	GO:CC	vesicle	GO:0031982
					cytoplasmic vesicle	GO:0031410
					intracellular vesicle	GO:0097708
4	NEU1	Sialidase-1	-0.52	GO:CC	vesicle	GO:0031982
					cytoplasmic vesicle	GO:0031410
					intracellular vesicle	GO:0097708
5	WDR81	WD repeat-containing protein 81	-0.53	GO:CC	vesicle	GO:0031982
					cytoplasmic vesicle	GO:0031410
					autophagosome	GO:0005776
					intracellular vesicle	GO:0097708
6	KLHL21	Kelch-like protein 21	-0.61	GO:CC	supramolecular polymer	GO:0099081
					cytoplasmic vesicle	GO:0031410
					intracellular vesicle	GO:0097708
					supramolecular complex	GO:0099080
					vesicle	GO:0031982
7	SYNE1	Nesprin-1	-0.68	GO:CC	supramolecular fiber	GO:0099512
					P-body	GO:0000932
					myofibril	GO:0030016

					contractile fiber	GO:0043292
					supramolecular polymer	GO:0099081
					sarcomere	GO:0030017
					supramolecular complex	GO:0099080
					supramolecular fiber	GO:0099512
8	COL1A1	Collagen, type I, α 1, isoform CRA_a	-0.73	GO:CC	vesicle	GO:0031982
					supramolecular fiber	GO:0099512
					supramolecular polymer	GO:0099081
					cytoplasmic vesicle	GO:0031410
					intracellular vesicle	GO:0097708
					supramolecular complex	GO:0099080
					collagen type I trimer	GO:0005584
9	RAP1GAP	Rap1 GTPase- activating protein 1	-0.74	GO:CC	cytoplasmic vesicle	GO:0031410
					vesicle	GO:0031982
					intracellular vesicle	GO:0097708
10	KRT4	Keratin, type II cytoskeletal 4	-1.23	GO:CC	supramolecular fiber	GO:0099512
					supramolecular polymer	GO:0099081
					supramolecular complex	GO:0099080

* Showing enrichment result from Gene Ontology Biological Process (GO:BP) and Cellular Component (GO:CC) databases with term size < 300 genes and overlap size > 10 genes.

Table S2B. Properties of the 17 DEGs that define the anti-cytokine signature derived from the transcriptome of SARS-CoV-2-infected A549-ACE2 cells

Index	Gene name	Protein name	Log ₂ Fold Change	P _{adjusted}	Database	GO Annotation	GO number
1	EGR1	Early growth response protein	6.62	0.00E+00	GO:BP	cytokine-mediated signaling pathway	GO:0019221
						cellular response to cytokine stimulus	GO:0071345
2	IFNB1	Interferon β	5.76	1.15E-28	GO:BP	cytokine-mediated signaling pathway	GO:0019221
						cellular response to cytokine stimulus	GO:0071345
						regulation of response to external stimulus	GO:0032101
						positive regulation of immune system process	GO:0002684
3	CXCL2	C-X-C motif chemokine	5.27	0.00E+00	GO:BP	cytokine-mediated signaling pathway	GO:0019221
						cellular response to cytokine stimulus	GO:0071345
4	NFKBIA	NF κ B inhibitor α	5.23	0.00E+00	GO:BP	cytokine-mediated signaling pathway	GO:0019221
						cellular response to cytokine stimulus	GO:0071345
						regulation of response to external stimulus	GO:0032101
5	SELE	E-selectin	4.85	1.59E-25	GO:BP	regulation of response to external stimulus	GO:0032101
						positive regulation of immune system process	GO:0002684
6	IL8	Multifunctional fusion protein [Includes: Interleukin-8]	4.85	0.00E+00	GO:BP	cytokine-mediated signaling pathway	GO:0019221
						cellular response to cytokine stimulus	GO:0071345
						regulation of response to external stimulus	GO:0032101
						positive regulation of immune system process	GO:0002684
7	IRF7	Interferon regulatory factor 7	4.81	2.69E-97	GO:BP	cytokine-mediated signaling pathway	GO:0019221
						cellular response to cytokine stimulus	GO:0071345
						regulation of response to external stimulus	GO:0032101
						positive regulation of immune system process	GO:0002684
8	IFITM1	Interferon induced transmembrane protein 1	4.58	3.21E-47	GO:BP	cytokine-mediated signaling pathway	GO:0019221
						cellular response to cytokine stimulus	GO:0071345
9	NFIL3	Nuclear factor interleukin-3-	4.22	0.00E+00	GO:BP	cellular response to cytokine stimulus	GO:0071345

		regulated protein					
10	TNF	Tumor necrosis factor	4.16	3.70E-29	GO:BP	cytokine-mediated signaling pathway	GO:0019221
						cellular response to cytokine stimulus	GO:0071345
						regulation of response to external stimulus	GO:0032101
						positive regulation of immune system process	GO:0002684
11	CXCL3	C-X-C motif chemokine 3	4.03	0.00E+00	GO:BP	cytokine-mediated signaling pathway	GO:0019221
						cellular response to cytokine stimulus	GO:0071345
12	SOCS1	Suppressor of cytokine signaling 1	4.02	1.48E-16	GO:BP	cytokine-mediated signaling pathway	GO:0019221
						cellular response to cytokine stimulus	GO:0071345
						regulation of response to external stimulus	GO:0032101
						positive regulation of immune system process	GO:0002684
13	CD274	Programmed cell death 1 ligand 1	4.01	1.20E-46	GO:BP	positive regulation of immune system process	GO:0002684
14	IL20RB	Interleukin-20 receptor subunit β	3.79	1.15E-34	GO:BP	cytokine-mediated signaling pathway	GO:0019221
						cellular response to cytokine stimulus	GO:0071345
						regulation of response to external stimulus	GO:0032101
15	CCL20	C-C motif chemokine 20	3.77	0.00E+00	GO:BP	cytokine-mediated signaling pathway	GO:0019221
						cellular response to cytokine stimulus	GO:0071345
						positive regulation of immune system process	GO:0002684
16	CCR6	C-C chemokine receptor type 6	3.66	1.60E-16	GO:BP	cytokine-mediated signaling pathway	GO:0019221
						cellular response to cytokine stimulus	GO:0071345
						regulation of response to external stimulus	GO:0032101
						positive regulation of immune system process	GO:0002684
17	HLA-F	HLA-F	3.49	3.59E-86	GO:BP	cytokine-mediated signaling pathway	GO:0019221
						cellular response to cytokine stimulus	GO:0071345
						regulation of response to external stimulus	GO:0032101
						positive regulation of immune system process	GO:0002684

* Gene name: gene symbol of the DEGs. Protein name: protein name of corresponding genes from UniProt¹ (Genes are ordered by log₂ fold change in descending order. see STAR*Methods for the definition of adjusted P. Showing enrichment results from GO Biological Process database with term size < 1,200 genes and overlap size > 10 genes. Log₂Fold Change: log₂ transformation of the fold change in gene expression level after viral infection; **Database:** Gene ontology (GO) database used. BP refers to biological process, CC refers to cellular component; **Term:** name of the gene set in the GO database; **GO number:** the index of the GO term. * Genes are ordered by descending log₂Fold Change.

Table S3A. 263 compounds with potential antiviral activity against SARS-CoV-2 infected A549 cells and corresponding CMap scores (all > 90)

Index	Compound name	CMap ID	CMap score	Mechanism of Action (MOA)
1	Salmeterol	BRD-A01320529	100.00	Adrenergic receptor agonist
2	Avrainvillamide-analog-5	BRD-A70731303	99.99	nucleophosmin inhibitor
3	Terbutaline	BRD-A50157456	99.98	Adrenergic receptor agonist
4	Oxybutynin	BRD-A65013509	99.98	Acetylcholine receptor antagonist
5	Leflunomide	BRD-K78692225	99.98	Dihydroorotate dehydrogenase inhibitor, PDGFR receptor inhibitor
6	GS-39783	BRD-K75478907	99.98	GABA receptor modulator
7	nTZDpa	BRD-K54708045	99.98	PPAR receptor agonist
8	n-arachidonyl-GABA	BRD-K06024458	99.98	cannabinoid receptor agonist
9	Salicin	BRD-K64614248	99.98	Anti-inflammatory
10	SR-27897	BRD-K35629949	99.98	CCK receptor antagonist
11	Thiotepa	BRD-K09631521	99.98	Cytochrome P450 inhibitor
12	Brazilin	BRD-A83326220	99.98	Nitric oxide production inhibitor
13	Stavudine	BRD-K93880783	99.98	DNA directed DNA polymerase inhibitor, Reverse transcriptase inhibitor
14	Oxiconazole	BRD-K23369905	99.98	Bacterial cell wall synthesis inhibitor
15	Mirtazapine	BRD-A64977602	99.98	Adrenergic receptor antagonist, Serotonin receptor antagonist
16	Liothyronine	BRD-K89152108	99.98	Thyroid hormone stimulant
17	Bergenin	BRD-A15034104	99.98	Interleukin inhibitor
18	Chlorpromazine	BRD-K89997465	99.98	Dopamine receptor antagonist
19	Fludarabine	BRD-K66788707	99.96	DNA synthesis inhibitor, DNA repair enzyme inhibitor, Purine antagonist
20	Iodophenpropit	BRD-K51918615	99.96	Histamine receptor antagonist
21	SA-94315	BRD-K20197062	99.96	Caspase inhibitor
22	L-733060	BRD-K15791587	99.96	Tachykinin antagonist
23	Tetrahydrobiopterin	BRD-A67605442	99.96	Nitric oxide (NO) stimulant, NO synthase stimulant, Phenylalanine 4-hydroxylase stimulant
24	Duloxetine	BRD-K71103788	99.96	Serotonin and norepinephrine reuptake inhibitor
25	PSB-36	BRD-A70407468	99.96	Adenosine receptor antagonist
26	CGP-7930	BRD-K65786282	99.95	GABA receptor positive allosteric modulator
27	Ochratoxin-a	BRD-K39944607	99.95	Phenylalanyl tRNA synthetase inhibitor
28	Alfacalcidol	BRD-K93433262	99.94	Vitamin D receptor agonist
29	Molsidomine	BRD-K35531059	99.94	Guanylyl cyclase activator
30	NGB-2904	BRD-K05181084	99.94	Dopamine receptor antagonist
31	BH3I-1	BRD-A38913120	99.93	BCL inhibitor
32	Isotretinoin	BRD-K76723084	99.93	Retinoid receptor agonist
33	Lonidamine	BRD-K96670504	99.92	Glucokinase inhibitor
34	L-741626	BRD-K05181463	99.91	Dopamine receptor antagonist
35	PG-9	BRD-A70268693	99.91	Acetylcholine receptor agonist
36	GSK-1059615	BRD-K06750613	99.90	PI3K inhibitor
37	Chenodeoxycholic-acid	BRD-K18135438	99.90	11- β -HSD1 inhibitor, FXR agonist
38	Edrophonium	BRD-K81128206	99.89	Acetylcholinesterase inhibitor
39	Nilotinib	BRD-K81528515	99.89	ABL inhibitor, BCR-ABL kinase inhibitor
40	5-nonyloxytryptamine	BRD-K08219523	99.88	Serotonin receptor agonist
41	Tribenoside	BRD-A60294240	99.88	Anti-inflammatory, Capillary stabilizing agent
42	Meclozine	BRD-A50311610	99.85	CAR agonist
43	Azathioprine	BRD-K32821942	99.85	Dehydrogenase inhibitor
44	HDAC3-selective	BRD-K29313308	99.84	HDAC inhibitor
45	MRS-1845	BRD-A32949107	99.84	Calcium channel blocker
46	KU-55933	BRD-K25311561	99.84	ATM kinase inhibitor
47	Arecidine	BRD-K63792901	99.84	Acetylcholine receptor agonist
48	Cortisone	BRD-A54487287	99.83	Glucocorticoid receptor agonist
49	Torin-1	BRD-K40175214	99.80	MTOR inhibitor, PI3K inhibitor
50	ENMD-2076	BRD-K68488863	99.79	FLT3 inhibitor, VEGFR inhibitor, Aurora kinase inhibitor
51	Aspirin	BRD-K11433652	99.79	Cyclooxygenase inhibitor
52	AS-703026	BRD-K89014967	99.74	MEK inhibitor
53	Razoxane	BRD-K07265709	99.74	Chelating agent, Topoisomerase inhibitor
54	Ibuprofen	BRD-A17655518	99.72	Cyclooxygenase inhibitor, NFkB pathway inhibitor

55	Demeclocycline	BRD-A75368507	99.71	Bacterial 30S ribosomal subunit inhibitor
56	KU-0063794	BRD-K67566344	99.71	MTOR inhibitor
57	Desoxycorticosterone	BRD-A75402480	99.69	Mineralocorticoid receptor agonist
58	Imipramine	BRD-K38436528	99.65	Norepinephrine and Serotonin transporter inhibitor
59	AS-605240	BRD-K41895714	99.63	PI3K inhibitor
60	OSI-027	BRD-K94294671	99.62	MTOR inhibitor
61	PD-0325901	BRD-K49865102	99.59	MEK inhibitor, MAPK inhibitor, Protein kinase inhibitor
62	PKC β -inhibitor	BRD-K89687904	99.59	PKC inhibitor
63	Fostamatinib	BRD-K20285085	99.58	SYK inhibitor
64	Semaxanib	BRD-K63504947	99.57	VEGFR inhibitor
65	SB-216641	BRD-K30867024	99.57	Serotonin receptor antagonist
66	Rescinnamine	BRD-K52930707	99.53	ACE inhibitor
67	Tolazoline	BRD-K46211610	99.53	Adrenergic receptor antagonist
68	Dactolisib	BRD-K12184916	99.51	MTOR inhibitor, PI3K inhibitor, Protein kinase inhibitor
69	GSK-1904529A	BRD-K04833372	99.50	IGF-1 inhibitor, IGF-1R inhibitor, Insulin receptor ligand
70	ML-9	BRD-K68402494	99.44	Myosin light chain kinase inhibitor
71	UNC-0321	BRD-K74236984	99.42	Histone lysine methyltransferase inhibitor
72	Pizotifen	BRD-K75958195	99.41	Serotonin receptor antagonist
73	Pterostilbene	BRD-K92870997	99.40	Cyclooxygenase inhibitor, PPAR receptor agonist
74	VER-155008	BRD-K32330832	99.39	HSP inhibitor
75	PIK-90	BRD-K99818283	99.35	PI3K inhibitor
76	Panobinostat	BRD-K02130563	99.34	HDAC inhibitor
77	Oleoylethanolamide	BRD-K66956375	99.31	Cannabinoid receptor agonist, Glucose dependent insulinotropic receptor agonist, Potassium channel blocker, PPAR receptor agonist
78	TC-2559	BRD-K67352070	99.30	Acetylcholine receptor agonist
79	Mosapride	BRD-A39052811	99.26	Serotonin receptor agonist
80	Dapsone	BRD-K62363391	99.21	Bacterial antifolate
81	BAY-36-7620	BRD-K54704028	99.20	Glutamate receptor antagonist
82	Emetine	BRD-A25687296	99.20	Protein synthesis inhibitor
83	Arecaidine	BRD-K23922020	99.19	Acetylcholine receptor agonist
84	Apicidin	BRD-K64606589	99.18	HDAC inhibitor
85	Niacin	BRD-K61993165	99.16	NAD precursor with lipid lowering effect, vitamin B
86	Entinostat	BRD-K77908580	99.16	HDAC inhibitor
87	Elesclomol	BRD-K82135108	99.15	Oxidative stress inducer
88	BMY-14802	BRD-A15435692	99.14	Sigma receptor antagonist
89	Proxymetacaine	BRD-K79116891	99.14	Sodium channel blocker
90	Zamifenacin	BRD-K80451230	99.14	Acetylcholine receptor antagonist
91	Anandamide	BRD-K78280988	99.12	Cannabinoid receptor agonist
92	Temsirolimus	BRD-A62025033	99.10	MTOR inhibitor
93	Desmethylclozapine	BRD-K10042277	99.07	Acetylcholine receptor agonist
94	QL-XII-47	BRD-U86922168	99.03	BTK inhibitor, Cytoplasmic tyrosine protein kinase BMX inhibitor
95	PI-103	BRD-K67868012	99.03	MTOR inhibitor, PI3K inhibitor
96	Eugenol	BRD-K32977963	99.01	Androgen receptor antagonist
97	SKF-81297	BRD-A09828896	98.98	Dopamine receptor agonist
98	2-aminopurine	BRD-K35128472	98.97	Serine/threonine kinase inhibitor
99	GBR-12783	BRD-K92015269	98.97	Dopamine uptake inhibitor
100	Mephentoin	BRD-A83937277	98.96	Hydantoin antiepileptic
101	Terfenadine	BRD-A06352418	98.89	Histamine receptor antagonist
102	KIN001-127	BRD-A29901043	98.89	ITK inhibitor
103	GBR-12935	BRD-K50135270	98.88	Dopamine uptake inhibitor
104	Flavanone	BRD-A07824748	98.74	11- β -HSD1 inhibitor
105	VU-0366037-2	BRD-K39823328	98.73	Glutamate receptor modulator
106	Ioxaglic-acid	BRD-K79124250	98.68	Radiopaque medium
107	FR-122047	BRD-K30990140	98.65	Cyclooxygenase inhibitor
108	WZ-3146	BRD-K73293050	98.61	EGFR inhibitor
109	Droxinostat	BRD-K11558771	98.60	HDAC inhibitor
110	Cimaterol	BRD-A65440446	98.56	Adrenergic receptor agonist
111	SCH-23390	BRD-K45435259	98.48	Dopamine receptor antagonist
112	Ribavirin	BRD-A96255180	98.45	Antiviral
113	Mycophenolate-mofetil	BRD-K92428153	98.41	Dehydrogenase inhibitor, Hydroxycarboxylic acid receptor agonist, Immunosuppressant, Inosine monophosphate dehydrogenase inhibitor, Inositol monophosphatase inhibitor
114	Linsitinib	BRD-K08589866	98.37	IGF-1 inhibitor
115	LY-288513	BRD-K24675965	98.28	CCK receptor antagonist
116	Wiskostatin	BRD-A18579359	98.25	Neural Wiskott-Aldrich syndrome protein inhibitor

117	AG-879	BRD-K59469039	98.23	Angiogenesis inhibitor, Tyrosine kinase inhibitor, VEGFR inhibitor
118	BIX-01338	BRD-K26863634	98.21	Histone lysine methyltransferase inhibitor
119	Arcyriaflavin-a	BRD-K72726508	98.20	CDK inhibitor
120	AY-9944	BRD-K03642198	98.15	Hedgehog pathway modulator
121	NU-7026	BRD-K09537769	98.15	DNA dependent protein kinase inhibitor, MTOR inhibitor, PI3K inhibitor
122	GW-9662	BRD-K93258693	98.08	PPAR receptor antagonist
123	APHA-compound-8	BRD-K74733595	98.07	HDAC inhibitor
124	Mefenamic-acid	BRD-K92778217	98.00	Cyclooxygenase inhibitor
125	Heliomycin	BRD-K64517075	98.00	ATP synthase inhibitor
126	PP-30	BRD-K30677119	97.98	RAF inhibitor
127	NVP-TAE684	BRD-K50140147	97.96	ALK inhibitor
128	Ropivacaine	BRD-K50938786	97.64	Sodium channel blocker
129	MK-5108	BRD-K53665955	97.59	Aurora kinase inhibitor
130	Ciclacillin	BRD-K89046952	97.54	Bacterial cell wall synthesis inhibitor
131	Sulfafurazole	BRD-K50859149	97.43	Bacterial antifolate
132	Dephostatin	BRD-K60274257	97.43	Tyrosine phosphatase inhibitor
133	Entacapone	BRD-K83636919	97.31	Catechol O methyltransferase inhibitor
134	Oxfendazole	BRD-A33447119	97.21	Anthelmintic
135	Rottlerin	BRD-K03816923	97.11	MAP kinase inhibitor, Protein kinase inhibitor
136	Desipramine	BRD-K60762818	97.10	Tricyclic antidepressant
137	Perospirone	BRD-K85503079	97.10	Dopamine and serotonin receptors' antagonist
138	Pimozide	BRD-K01292756	97.10	Dopamine receptor antagonist
139	Ceforanide	BRD-K37848908	97.00	Penicillin binding protein inhibitor
140	Equilin	BRD-K04046242	96.99	Estrogen receptor agonist
141	SB-590885	BRD-K01253243	96.95	RAF inhibitor
142	LY-2140023	BRD-K49519144	96.93	Glutamate receptor agonist
143	Glipizide	BRD-K12219985	96.92	Sulfonylurea
144	Moracizine	BRD-K21548250	96.91	Sodium channel blocker
145	Kavain	BRD-A75455249	96.82	Calcium channel modulator, Sodium channel blocker
146	Wortmannin	BRD-A11678676	96.81	PI3K inhibitor
147	Decitabine	BRD-K79254416	96.67	DNA methyltransferase inhibitor
148	Metformin	BRD-K79602928	96.61	Insulin sensitizer
149	Eicosatrienoic-acid	BRD-K63913457	96.58	Vasodilator
150	Raloxifene	BRD-K63828191	96.58	Estrogen receptor antagonist, Selective estrogen receptor modulator (SERM)
151	Ezetimibe	BRD-A41519720	96.57	Niemann-Pick C1-like 1 protein antagonist, Cholesterol inhibitor
152	NBI-27914	BRD-K61177364	96.54	CRF receptor antagonist
153	RS-67333	BRD-K46142322	96.52	Serotonin receptor partial agonist
154	BMS-191011	BRD-K95609758	96.46	Potassium channel activator
155	H-7	BRD-A55756846	96.39	PKA inhibitor
156	VU-0404997-2	BRD-A34208323	96.39	Glutamate receptor modulator
157	Cisapride	BRD-K06895174	96.23	Serotonin receptor agonist
158	Y-134	BRD-K94832621	96.20	Estrogen receptor antagonist
159	Metrizamide	BRD-A45543382	95.98	Radiopaque medium
160	Dydrogesterone	BRD-K68620903	95.94	Progesterone receptor agonist
161	Altrenogest	BRD-A27554692	95.93	Progestogen hormone
162	Homosalate	BRD-A34751532	95.90	HSP inducer
163	Bosutinib	BRD-K99964838	95.89	ABL inhibitor, BCR-ABL kinase inhibitor, SRC inhibitor
164	Puromycin	BRD-A28970875	95.88	Protein synthesis inhibitor
165	Methimazole	BRD-K54416256	95.71	Antithyroid
166	ALW-II-38-3	BRD-K68191783	95.60	Ephrin inhibitor
167	SN-38	BRD-A36630025	95.51	Topoisomerase inhibitor
168	Ipratropium	BRD-A05352148	95.50	Acetylcholine receptor antagonist
169	TGX-221	BRD-A41692738	95.47	PI3K inhibitor
170	Homoharringtonine	BRD-K76674262	95.43	Protein synthesis inhibitor
171	Metergoline	BRD-A30435184	95.42	Dopamine receptor agonist, Serotonin receptor antagonist
172	WZ-4-145	BRD-U25771771	95.41	EGFR inhibitor
173	Mercaptopurine	BRD-K91601245	95.33	Immunosuppressant, Protein synthesis inhibitor, Purine antagonist
174	Calmidazolium	BRD-A98283014	95.28	Calcium channel blocker, Calmodulin antagonist
175	Mesna	BRD-M40783228	95.21	Antioxidant
176	SDZ-205-557	BRD-K15868788	95.20	Serotonin receptor antagonist
177	Procyclidine	BRD-A31800922	95.16	Acetylcholine receptor antagonist
178	Amiodarone	BRD-K17561142	95.15	Potassium channel blocker

179	Midodrine	BRD-A79981887	95.14	Adrenergic receptor agonist
180	Mepireserpate	BRD-A71765365	95.11	Catecholamine depleting sympatholytic
181	SA-792728	BRD-K20755323	95.06	Sphingosine kinase inhibitor
182	Brompheniramine	BRD-A68723818	94.90	Histamine receptor antagonist
183	Sumatriptan	BRD-K50938287	94.83	Serotonin receptor agonist
184	Gemcitabine	BRD-K15108141	94.82	Ribonucleotide reductase inhibitor
185	JAK3-Inhibitor-II	BRD-K52850071	94.81	JAK inhibitor
186	CHEMBL-374350	BRD-K59962020	94.79	NFkB pathway inhibitor
187	Vorinostat	BRD-K81418486	94.70	HDAC inhibitor
188	Dipyridamole	BRD-K86301799	94.48	Phosphodiesterase inhibitor
189	JNJ-16259685	BRD-K64670467	94.47	Glutamate receptor antagonist
190	VU-0415374-1	BRD-K83010055	94.46	Glutamate receptor modulator
191	Pidorubicine	BRD-K04548931	94.42	Topoisomerase inhibitor
192	KU-C103443N	BRD-A81402010	94.22	CDC inhibitor, Rho associated kinase inhibitor
193	Dichlorobenzamil	BRD-K12906962	94.16	Sodium/calcium exchange inhibitor
194	Mepacrine	BRD-A45889380	94.14	Cytokine production inhibitor, NFkB pathway inhibitor, TP53 activator
195	E-4031	BRD-K41713976	93.96	Potassium channel blocker
196	Narciclasine	BRD-K06792661	93.94	Cofilin signaling pathway activator, LIM kinase activator, Rho associated kinase activator
197	Mesoridazine	BRD-A14395271	93.80	Dopamine receptor antagonist
198	Tranlycypromine	BRD-A43974575	93.79	Monoamine oxidase inhibitor
199	Lypressin	BRD-K93331255	93.76	Vasopressin receptor agonist
200	Reserpine	BRD-K95921201	93.69	Vesicular monoamine transporter inhibitor
201	Abiraterone	BRD-K55301415	93.64	17,20 lyase inhibitor, Androgen biosynthesis inhibitor, Cytochrome P450 inhibitor, Steroid sulfatase inhibitor
202	I-OMe-AG-538	BRD-K35377380	93.59	IGF-1 inhibitor
203	Somatostatin	BRD-K14681867	93.48	Somatostatin receptor agonist
204	Splitomycin	BRD-K27710560	93.37	SIRT inhibitor
205	AM-281	BRD-K59419204	93.34	Cannabinoid receptor antagonist
206	Sphingosine	BRD-K62959606	93.32	Ceramidase inhibitor
207	Hydroxycholesterol	BRD-A36707673	93.30	LXR agonist
208	TPCA-1	BRD-K51575138	93.29	IKK inhibitor
209	FGIN-1-27	BRD-K09778810	93.26	Inositol monophosphatase inhibitor
210	Trichostatin-a	BRD-K68202742	93.06	HDAC inhibitor, CDK activator, ID1 inhibitor
211	Hexylresorcinol	BRD-K99946902	92.99	Local anesthetic
212	Epicatechin	BRD-K50660797	92.96	Bacterial DNA gyrase inhibitor, Cyclooxygenase inhibitor, DNA polymerase inhibitor
213	RS-17053	BRD-K76840893	92.95	Adrenergic receptor antagonist
214	NSC-663284	BRD-K03109492	92.78	CDC inhibitor
215	L-165041	BRD-K40656405	92.55	PPAR receptor agonist
216	ML-7	BRD-K93201660	92.46	Myosin light chain kinase inhibitor
217	Alisertib	BRD-K75295174	92.44	Aurora kinase inhibitor
218	GR-127935	BRD-K11911061	92.37	Serotonin receptor antagonist
219	Clobenpropit	BRD-K71430621	92.36	Histamine receptor antagonist
220	NNC-55-0396	BRD-K78122587	92.31	T-type calcium channel blocker
221	Barasertib	BRD-K63923597	92.27	Aurora kinase inhibitor
222	Benidipine	BRD-A35519318	92.25	Calcium channel blocker
223	Sertraline	BRD-K82036761	92.24	Serotonin receptor antagonist
224	ZM-447439	BRD-K72703948	92.16	Aurora kinase inhibitor
225	BIBX-1382	BRD-K70914287	92.15	EGFR inhibitor, Tyrosine kinase inhibitor
226	Immethridine	BRD-K49519092	92.15	Histamine receptor agonist
227	MR-16728	BRD-A30590053	92.15	Acetylcholine release enhancer, Acetylcholine release stimulant
228	Heraclenol	BRD-A77050075	92.11	Vitamin K antagonist
229	NU-7441	BRD-K00337317	92.10	DNA dependent protein kinase inhibitor, P-glycoprotein inhibitor
230	Hyoscyamine	BRD-K40530731	91.85	Acetylcholine receptor antagonist
231	m-chlorophenylbiguanide	BRD-K36965586	91.76	Serotonin receptor agonist
232	Prostaglandin-b2	BRD-K82865713	91.75	cAMP inhibitor
233	BML-ST330	BRD-A77118605	91.59	Phospholipase inhibitor
234	STO-609	BRD-K52620403	91.57	Calmodulin antagonist
235	Tyrphostin-AG-556	BRD-K14441456	91.50	EGFR inhibitor
236	Corynanthine	BRD-K06467078	91.46	Adrenergic receptor antagonist
237	PD-102807	BRD-A89337244	91.31	Acetylcholine receptor antagonist
238	Norgestrel	BRD-A50928468	91.25	Progesterone receptor agonist
239	Telmisartan	BRD-K73999723	91.25	Angiotensin receptor antagonist

240	BMY-45778	BRD-K84895041	91.22	IP1 prostacyclin receptor agonist
241	Dihydrosamidin	BRD-K63945320	91.19	Phospholipase inhibitor, Nitric oxide production inhibitor, platelet activating factor receptor antagonist
242	HG-6-64-01	BRD-U37049823	91.09	RAF inhibitor
243	KUC104502N	BRD-K24538644	91.06	—
244	Formestane	BRD-A31801025	91.00	Aromatase inhibitor
245	BRD-K64835161	BRD-K64835161	90.93	—
246	M2-PK-activator	BRD-K80672993	90.89	—
247	Cetraxate	BRD-K48932581	90.81	Mucus protecting agent
248	Terbinafine	BRD-K68132782	90.76	Fungal squalene epoxidase inhibitor
249	Phosphodiesterase-V-inhibitor-II	BRD-K68873215	90.69	Phosphodiesterase inhibitor
250	Ponalrestat	BRD-K68332390	90.68	Aldose reductase inhibitor
251	Phenytoin	BRD-K55930204	90.67	Hydantoin antiepileptic
252	Phylloquinone	BRD-A55815733	90.64	Vitamin K, Γ carboxylase enzyme
253	AZD-8055	BRD-K69932463	90.64	MTOR inhibitor
254	PHA-665752	BRD-K95435023	90.53	c-Met inhibitor
255	PD-184352	BRD-K05104363	90.52	MEK inhibitor
256	RU-28318	BRD-A92585442	90.43	Cytochrome P450 inhibitor
257	Fenoldopam	BRD-A50684349	90.38	Dopamine receptor agonist
258	Camptothecin	BRD-A30437061	90.32	Topoisomerase inhibitor
259	Tretinoin	BRD-K06926592	90.31	Retinoid receptor agonist, Retinoid receptor ligand
260	Metixene	BRD-A33711280	90.16	Acetylcholine receptor antagonist
261	Tetrahydropalmatine	BRD-A43940795	90.12	Serotonin release inhibitor
262	YM-976	BRD-K12932420	90.09	Phosphodiesterase inhibitor
263	Alaproclate	BRD-A14966924	90.03	Serotonin receptor antagonist

Table S3B. 275 compounds with CMap scores < -90, which can potentially elicit anti-cytokine activity against hyperinflammation in SARS-CoV-2-infected A549-ACE2 cells

Index	Compound name	CMap ID	CMap score	Mechanism of Action (MOA)
1	n-(3-acetamidophenyl)-3-chlorobenzamide	BRD-K61217870	-100	Glutamate receptor antagonist
2	BI-78D3	BRD-K73982490	-99.98	JNK inhibitor
3	Xaliproden	BRD-K88358234	-99.98	Serotonin receptor agonist
4	Rhamnetin	BRD-K37206356	-99.98	HDAC inhibitor
5	MR-16728	BRD-A30590053	-99.98	Acetylcholine release enhancer or stimulant
6	Palonosetron	BRD-K08924299	-99.98	Serotonin receptor antagonist
7	Clarithromycin	BRD-K49668410	-99.98	Bacterial 50S ribosomal subunit inhibitor
8	SAL-1	BRD-K40213712	-99.98	Adenosine receptor antagonist
9	Nimodipine	BRD-A58048407	-99.98	Calcium channel blocker
10	Isoliquiritigenin	BRD-K33583600	-99.98	Guanylate cyclase activator
11	Cyclazosin	BRD-A37837077	-99.98	Adrenergic receptor antagonist
12	Eicosatetraynoic-acid	BRD-K06080977	-99.98	Cyclooxygenase inhibitor, Lipooxygenase inhibitor
13	Oxantel	BRD-K66019333	-99.96	Anthelmintic
14	Nor-binaltorphimine	BRD-A11135865	-99.96	Opioid receptor antagonist
15	PCA-4248	BRD-A29289453	-99.95	Platelet activating factor receptor antagonist
16	Ketanserin	BRD-K49671696	-99.95	Serotonin receptor antagonist
17	Tyrphostin-AG-82	BRD-K03670461	-99.94	EGFR inhibitor
18	Azelastine	BRD-A68888262	-99.94	Histamine receptor antagonist
19	Diethylstilbestrol	BRD-K45330754	-99.93	Estrogen receptor agonist
20	Raltegravir	BRD-K05658747	-99.93	HIV integrase inhibitor
21	KI-16425	BRD-A25569250	-99.93	Lysophosphatidic acid receptor antagonist
22	Pyroxamide	BRD-K11663430	-99.93	HDAC inhibitor
23	Maprotiline	BRD-K03319035	-99.93	Norepinephrine reuptake inhibitor, Tricyclic antidepressant
24	Reserpine-acid	BRD-K32755366	-99.91	Norepinephrine transporter inhibitor
25	Fostamatinib	BRD-K20285085	-99.91	SYK inhibitor
26	Y-27632	BRD-K44084986	-99.91	Rho associated kinase inhibitor
27	Dexketoprofen	BRD-K43764301	-99.9	Cyclooxygenase inhibitor
28	EMF-bca1-60	BRD-K68437527	-99.9	caspase inhibitor
29	Fluphenazine	BRD-K55127134	-99.9	Dopamine receptor antagonist
30	Gabazine	BRD-K93280214	-99.89	GABA receptor antagonist
31	α -estradiol	BRD-A60070924	-99.88	Estrogen receptor agonist

32	Benzydamine	BRD-K76133116	-99.88	Membrane integrity inhibitor, Prostanoid receptor antagonist, Prostanoid receptor inhibitor
33	Navitoclax	BRD-K82746043	-99.88	BCL inhibitor
34	Nifurtimox	BRD-A00100033	-99.86	DNA inhibitor
35	Thenoyltrifluoroacetone	BRD-K00959089	-99.86	Chelating agent
36	NVP-AUY922	BRD-K41859756	-99.86	HSP inhibitor
37	BRD-K64835161	BRD-K64835161	-99.85	NA
38	Atorvastatin	BRD-U88459701	-99.85	HMGCR (HMG CoA reductase) inhibitor
39	Securinine	BRD-A25775766	-99.82	GABA receptor antagonist, TP53 activator
40	Nikkomycin	BRD-A74771556	-99.82	Chitin inhibitor
41	Zuclopenthixol	BRD-K28761384	-99.78	Dopamine receptor antagonist
42	Temozolomide	BRD-K32107296	-99.78	DNA alkylating agent
43	HY-11007	BRD-K97056771	-99.77	BCR-ABL kinase inhibitor
44	Salsolinol	BRD-K99595596	-99.74	Monoamine oxidase inhibitor, Tyrosine hydroxylase inhibitor
45	SCH-28080	BRD-K55748775	-99.73	ATPase inhibitor
46	Retinol	BRD-K13927029	-99.72	Retinoid receptor ligand
47	SB-216763	BRD-K59184148	-99.72	Glycogen synthase kinase inhibitor
48	YS-035	BRD-K06208435	-99.71	Calcium channel blocker
49	Bisoprolol	BRD-A89175223	-99.69	Adrenergic receptor antagonist
50	Carteolol	BRD-A42167015	-99.62	Adrenergic receptor antagonist
51	TER-14687	BRD-A33833419	-99.62	Inhibitor of translocation of PKCq in T cells
52	Selegiline	BRD-K86434416	-99.59	Monoamine oxidase inhibitor
53	Triptolide	BRD-A13122391	-99.58	RNA polymerase inhibitor
54	Lisuride	BRD-K88871508	-99.57	Dopamine receptor agonist
55	Topiramate	BRD-K29653726	-99.57	Carbonic anhydrase inhibitor, Glutamate receptor antagonist, Kainate receptor antagonist
56	Berbamine	BRD-K50464341	-99.55	Calmodulin antagonist
57	Hexamethylenamiloride	BRD-K40990712	-99.53	Sodium/hydrogen antiport inhibitor
58	MW-STK33-3B	BRD-K64310881	-99.52	Potassium channel activator
59	MLN-4924	BRD-K67844266	-99.5	Nedd activating enzyme inhibitor
60	EHNA	BRD-K27450477	-99.48	Adenosine deaminase inhibitor
61	Chlorprothixene	BRD-K59058766	-99.46	Dopamine receptor antagonist
62	DUP-697	BRD-K06221026	-99.45	Cyclooxygenase inhibitor
63	Chlorphenamine	BRD-A04553218	-99.45	Histamine receptor antagonist
64	NAS-181	BRD-A23683907	-99.38	Serotonin receptor antagonist
65	Linsitinib	BRD-K08589866	-99.37	IGF-1 inhibitor, insulin inhibitor, ARF6 and TBK1 activator
66	YC-1	BRD-K60476892	-99.34	Guanylyl cyclase activator
67	Olanzapine	BRD-K18895904	-99.32	Dopamine receptor/serotonin receptor antagonist
68	Orantinib	BRD-K91696562	-99.3	FGFR, VEGFR, PDGFR inhibitor
69	Phenelzine	BRD-K87024524	-99.3	Monoamine oxidase inhibitor
70	TGX-221	BRD-A41692738	-99.29	PI3K inhibitor
71	Latrepiridine	BRD-K55703048	-99.29	Glutamate receptor antagonist
72	PU-H71	BRD-K36529613	-99.28	HSP inhibitor
73	Bromocriptine	BRD-A69960130	-99.24	Dopamine receptor agonist
74	Syrosingopine	BRD-K14200658	-99.21	Vesicular monoamine transporter inhibitor
75	UNC-0321	BRD-K74236984	-99.21	Histone lysine methyltransferase inhibitor
76	BRD-A80383043	BRD-A80383043	-99.19	Glutamate receptor agonist and/or antagonist
77	Trifluoperazine	BRD-K89732114	-99.17	Dopamine receptor antagonist
78	AQ-RA741	BRD-K81729199	-99.16	Acetylcholine receptor antagonist
79	Bromfenac	BRD-K47679368	-99.14	Cyclooxygenase inhibitor
80	Oxaprozin	BRD-K25394294	-99.14	Cyclooxygenase inhibitor
81	CGS-20625	BRD-K68103045	-99.12	Benzodiazepine receptor agonist, GABA benzodiazepine site receptor partial agonist
82	Rucaparib	BRD-K88560311	-99.11	PARP inhibitor
83	o-3M3FBS	BRD-K46384212	-99.09	phospholipase activator
84	L-655240	BRD-K89402695	-99.07	Thromboxane receptor antagonist
85	L-750667	BRD-K28806945	-99.04	Dopamine receptor antagonist
86	Daunorubicin	BRD-K43389675	-98.99	RNA synthesis inhibitor, Topoisomerase inhibitor
87	Profenamine	BRD-A16311756	-98.98	Butyrylcholinesterase inhibitor, Cholinergic receptor antagonist
88	Saracatinib	BRD-K19540840	-98.97	SRC inhibitor
89	Trazodone	BRD-K70778732	-98.96	Adrenergic receptor antagonist, Serotonin receptor antagonist, Serotonin reuptake inhibitor
90	Valproic-acid	BRD-K41260949	-98.93	HDAC inhibitor
91	Medetomidine	BRD-A66563878	-98.93	Adrenergic receptor agonist
92	Piperine	BRD-K59522102	-98.92	Monoamine oxidase inhibitor

93	Pyrazinamide	BRD-K28667793	-98.83	Fatty acid synthase inhibitor
94	Fraxidin	BRD-K66944906	-98.83	Carbonic anhydrase inhibitor
95	Larixinic-acid	BRD-K40619305	-98.78	Compound that interacts with metal centers
96	Midodrine	BRD-A79981887	-98.74	Adrenergic receptor agonist
97	XAV-939	BRD-K12762134	-98.73	Tankyrase inhibitor
98	AICA-ribonucleotide	BRD-A67373739	-98.7	AMPK activator
99	PIK-90	BRD-K99818283	-98.66	PI3K inhibitor
100	PNU-22394	BRD-K16551401	-98.63	Serotonin receptor agonist
101	AY-9944	BRD-K03642198	-98.62	Hedgehog pathway modulator
102	Gavestinel	BRD-K49890030	-98.59	Glutamate receptor antagonist
103	Foliosidine	BRD-A49734948	-98.54	Plant alkaloid
104	Naftopidil	BRD-A01787639	-98.48	Adrenergic receptor antagonist
105	GDC-0941	BRD-K52911425	-98.38	PI3K inhibitor
106	Clonidine	BRD-K98530306	-98.37	Adrenergic receptor agonist
107	CGP-54626	BRD-A55369275	-98.35	GABA receptor antagonist
108	Tosyllysyl-chloromethyl-ketone	BRD-K10136726	-98.32	Chymotrypsin inhibitor
109	Indatraline	BRD-K01649396	-98.31	Norepinephrine transporter inhibitor
110	9-methyl-5H-6-thia-4,5-diaza-chrysene-6,6-dioxide	BRD-K14696368	-98.28	NFkB pathway inhibitor
111	NNC-05-2090	BRD-K85015012	-98.27	GAT inhibitor, GABA uptake inhibitor
112	3-matida	BRD-A87125127	-98.19	Glutamate receptor antagonist
113	Phenothiazine	BRD-K59597909	-98.17	Dopamine receptor antagonist
114	Piribedil	BRD-K47936004	-98.16	Dopamine receptor agonist
115	Mebeverine	BRD-A09467419	-98.09	Acetylcholine receptor antagonist
116	GANT-58	BRD-K64451768	-98.06	GLI antagonist
117	RITA	BRD-K00317371	-98.03	MDM inhibitor
118	Pirenperone	BRD-K25224017	-98.01	Serotonin receptor antagonist
119	KIN001-244	BRD-K09186807	-98.01	Phosphoinositide dependent kinase inhibitor
120	Ozagrel	BRD-K19525698	-97.97	Thromboxane synthase inhibitor
121	PP-30	BRD-K30677119	-97.96	RAF inhibitor
122	CNQX	BRD-K53545112	-97.96	Glutamate receptor antagonist
123	STO-609	BRD-K52620403	-97.91	Calmodulin antagonist
124	Loperamide	BRD-K61250553	-97.74	Opioid receptor agonist
125	Dichloroacetic-acid	BRD-K13664374	-97.69	Pyruvate dehydrogenase kinase inhibitor
126	PI-103	BRD-K67868012	-97.66	MTOR inhibitor, PI3K inhibitor
127	Metoclopramide	BRD-K75641298	-97.54	Dopamine receptor and serotonin receptor antagonist
128	Spirolactone	BRD-K90027355	-97.54	Mineralocorticoid receptor antagonist
129	Loratadine	BRD-K82795137	-97.51	Histamine receptor antagonist
130	Pirfenidone	BRD-K96862998	-97.45	TGF β receptor inhibitor
131	ICI-89406	BRD-A03359064	-97.34	Adrenergic receptor antagonist
132	Clebopride	BRD-K17294426	-97.31	Dopamine receptor antagonist
133	Prostaglandin-a1	BRD-K04010869	-97.3	HSP inducer, NFkB pathway inhibitor
134	Butylparaben	BRD-K08287586	-97.27	DNA synthesis inhibitor
135	Testosterone	BRD-A48720949	-97.13	androgen receptor agonist
136	WZ-4002	BRD-K72420232	-97.11	EGFR inhibitor
137	PLX-4720	BRD-K16478699	-97.01	RAF inhibitor
138	Darinaparsin	BRD-K35723520	-97.01	Apoptosis stimulant
139	PTB1	BRD-K16554956	-96.94	AMPK activator
140	Alosetron	BRD-K46742498	-96.93	Serotonin receptor antagonist
141	U-99194	BRD-K70281171	-96.87	Dopamine receptor antagonist
142	Otenzepad	BRD-A00520476	-96.85	Acetylcholine receptor antagonist
143	Fursultiamine	BRD-A71157293	-96.84	Vitamin B
144	Piperacetazine	BRD-K16277217	-96.79	Dopamine receptor antagonist
145	SD-169	BRD-K91904471	-96.77	p38 MAPK inhibitor
146	Liothyronine	BRD-K89152108	-96.77	Thyroid hormone stimulant
147	Mepacrine	BRD-A45889380	-96.77	Cytokine production inhibitor, NFkB pathway inhibitor, TP53 activator
148	Nicotine	BRD-K05395900	-96.71	Acetylcholine receptor agonist
149	TG-101348	BRD-K12502280	-96.66	FLT3 inhibitor, JAK inhibitor
150	Quinpirole	BRD-A85280935	-96.54	Dopamine receptor agonist
151	Mafenide	BRD-K30649484	-96.53	Carbonic anhydrase inhibitor
152	Dephostatin	BRD-K60274257	-96.5	Tyrosine phosphatase inhibitor
153	Cisapride	BRD-K06895174	-96.49	Serotonin receptor agonist
154	Dicyclohexylurea	BRD-K81521265	-96.48	Epoxide hydrolase inhibitor
155	m-chlorophenylbiguanide	BRD-K36965586	-96.47	Serotonin receptor agonist

156	Auraptene	BRD-K85013741	-96.45	Nitric oxide production inhibitor
157	Alprenolol	BRD-A00993607	-96.44	Adrenergic receptor antagonist
158	TPCA-1	BRD-K51575138	-96.39	IKK inhibitor
159	Sertraline	BRD-K82036761	-96.37	Serotonin receptor antagonist
160	AC-55649	BRD-K93176058	-96.37	Retinoid receptor agonist
161	CDK1-5-inhibitor	BRD-K87932577	-96.35	CDK inhibitor, Glycogen synthase kinase inhibitor
162	D-64406	BRD-K27665173	-96.25	PDGFR receptor inhibitor
163	Fipronil	BRD-A50675702	-96.24	GABA gated chloride channel blocker
164	RO-25-6981	BRD-K51541829	-96.14	Ionotropic glutamate receptor antagonist, Monamine transporter modulator
165	BIIB021	BRD-K51967704	-96.11	HSP inhibitor
166	AZD-6482	BRD-K58772419	-96.1	PI3K inhibitor
167	EMD-386088	BRD-K47659338	-96.09	Serotonin receptor agonist
168	CITCO	BRD-K53263234	-96.07	CAR agonist
169	Exemestane	BRD-A73741725	-95.97	Aromatase inhibitor
170	GR-206	BRD-K00184207	-95.95	Aryl hydrocarbon receptor ligand
171	Dasatinib	BRD-K49328571	-95.91	BCR-ABL kinase inhibitor, Ephrin inhibitor, KIT inhibitor, PDGFR receptor inhibitor, SRC inhibitor, Tyrosine kinase inhibitor
172	MDM2-inhibitor	BRD-K84987553	-95.89	MDM inhibitor
173	Aminomethyltransferase	BRD-A28318179	-95.8	Nitric oxide synthase inhibitor
174	BRL-52537	BRD-A37347161	-95.7	Opioid receptor agonist
175	Amoxapine	BRD-K02265150	-95.68	Norepinephrine reuptake inhibitor
176	RO-08-2750	BRD-K00486786	-95.68	NGF binding inhibitor
177	Flutamide	BRD-K28307902	-95.68	Androgen receptor antagonist
178	DMBI	BRD-K96084870	-95.63	PDGFR receptor inhibitor, VEGFR inhibitor
179	Carmoxirole	BRD-K82484965	-95.61	Dopamine receptor agonist
180	Taurodeoxycholic-acid	BRD-K33572481	-95.59	Bile acid
181	Bupropion	BRD-A05186015	-95.57	Dopamine uptake inhibitor
182	Chlordiazepoxide	BRD-K86595100	-95.49	Benzodiazepine receptor agonist
183	Roscovitine	BRD-K07691486	-95.37	CDK inhibitor
184	ALW-II-38-3	BRD-K68191783	-95.33	Ephrin inhibitor
185	Ornidazole	BRD-A42759514	-95.22	Antiprotozoal
186	Iodophenpropit	BRD-K51918615	-95.18	Histamine receptor antagonist
187	Prima-1-met	BRD-K49456190	-95.18	thioredoxin inhibitor
188	EI-247	BRD-K32710582	-95.17	IGF-1 inhibitor
189	MK-2206	BRD-K68065987	-95.16	AKT inhibitor
190	BMS-299897	BRD-K02950022	-95.14	γ secretase inhibitor
191	Promazine	BRD-K06980535	-95.11	Dopamine receptor antagonist
192	CGP-60474	BRD-K79090631	-95.09	CDK inhibitor
193	PF-04217903	BRD-K73319509	-95.06	c-Met inhibitor
194	Pantoprazole	BRD-A22380646	-95.02	ATPase inhibitor
195	Norgestimate	BRD-A04756508	-94.95	Progesterone receptor agonist
196	Mead-ethanolamide	BRD-K09764130	-94.82	Cannabinoid receptor agonist
197	CL-82198	BRD-K00675675	-94.73	Metalloproteinase inhibitor
198	HLI-373	BRD-K17349619	-94.73	MDM inhibitor
199	Nifedipine	BRD-K96354014	-94.71	Calcium channel blocker
200	Sildenafil	BRD-K50128260	-94.71	Phosphodiesterase inhibitor
201	ICI-199441	BRD-K73290745	-94.63	Opioid receptor agonist
202	Ipsapirone	BRD-K90574421	-94.61	Serotonin receptor agonist
203	Milrinone	BRD-K67080878	-94.49	Phosphodiesterase inhibitor
204	Cotinine	BRD-K94144010	-94.35	Nicotine metabolite
205	Etilefrine	BRD-A09925278	-94.23	Adrenergic receptor agonist
206	Thiopropazine	BRD-K08619574	-94.19	Dopamine receptor antagonist
207	Acadesine	BRD-A95696820	-94.15	AMPK activator
208	Danazol	BRD-A92537424	-94.09	Estrogen receptor antagonist, Progesterone receptor agonist
209	z-prolyl-prolinal	BRD-K60174629	-94.04	Prolyl endopeptidase inhibitor
210	Pravastatin	BRD-K60511616	-94.03	HMGCR inhibitor
211	PP-2	BRD-K95785537	-94.01	SRC inhibitor
212	BRD-K63784565	BRD-K63784565	-94.01	Topoisomerase inhibitor
213	Geldanamycin	BRD-A19500257	-93.9	HSP inhibitor
214	Verapamil	BRD-A09533288	-93.88	Calcium channel blocker
215	Amylocaine	BRD-A09062839	-93.70	Local anesthetic
216	Anagrelide	BRD-K62200014	-93.38	Phosphodiesterase inhibitor
217	JAK3-Inhibitor-II	BRD-K52850071	-93.37	JAK inhibitor
218	Felbamate	BRD-K99107520	-93.35	Glutamate receptor antagonist

219	BP-554	BRD-K45479396	-93.33	Serotonin receptor agonist
220	Dicycloverine	BRD-K68507560	-93.3	Acetylcholine receptor antagonist
221	Nicorandil	BRD-K97752965	-93.29	Nitric oxide donor, Potassium channel activator
222	SCH-442416	BRD-K46469693	-93.27	Adenosine receptor antagonist
223	Carpindolol	BRD-A15530910	-93.19	Adrenergic receptor antagonist, serotonin receptor antagonist
224	VU-0420363-1	BRD-K59633790	-92.96	SARS coronavirus 3C-like protease inhibitor
225	Oxybutynin	BRD-A65013509	-92.9	Acetylcholine receptor antagonist
226	SA-792541	BRD-K68143200	-92.8	CDC inhibitor
227	Dipropyl-5ct	BRD-K32645441	-92.74	Serotonin receptor agonist
228	Ticlopidine	BRD-K00603606	-92.72	Purinergic receptor antagonist
229	SDZ-WAG-994	BRD-A31007383	-92.71	Adenosine receptor agonist
230	Mepylcaine	BRD-K65417056	-92.69	Local anesthetic
231	Cycloserine	BRD-K87226815	-92.58	Bacterial cell wall synthesis inhibitor
232	KIN001-127	BRD-A29901043	-92.54	ITK inhibitor
233	Enrofloxacin	BRD-K76534306	-92.54	Bacterial DNA gyrase inhibitor
234	Alverine	BRD-K89055274	-92.52	Muscle relaxant
235	Bepidil	BRD-A91008255	-92.5	Calcium channel or L-type Ca ⁺⁺ channel blocker
236	Nefazodone	BRD-K90789829	-92.39	Adrenergic inhibitor, Norepinephrine reuptake inhibitor, Serotonin receptor antagonist, Serotonin reuptake inhibitor
237	PSB-11	BRD-K10177585	-92.33	Adenosine receptor antagonist
238	Acetyl-geranyl-cysteine	BRD-U01690642	-92.32	Isoprenylated protein methylation inhibitor
239	Estradiol	BRD-A18917088	-92.31	Contraceptive agent, Estrogen receptor agonist
240	Secoisolariciresinol	BRD-K91733562	-92.2	Antioxidant
241	Prostaglandin	BRD-K09436313	-92.13	Prostanoid receptor antagonist
242	Alfuzosin	BRD-A09056319	-92.11	Adrenergic receptor antagonist
243	Oxybenzone	BRD-K59037100	-92.1	Lipase inhibitor
244	KIN001-220	BRD-K53561341	-91.98	Aurora kinase inhibitor
245	AZD-8055	BRD-K69932463	-91.85	MTOR inhibitor
246	Toltrazuril	BRD-K64514229	-91.83	Antiprotozoal
247	Mepyramine	BRD-K97564742	-91.79	Histamine receptor antagonist
248	Edaravone	BRD-K35458079	-91.74	Nootropic agent
249	FIT	BRD-K17896185	-91.6	Opioid receptor agonist
250	Dopamine	BRD-K43887077	-91.51	Dopamine receptor agonist
251	Tolterodine	BRD-K54316499	-91.49	Acetylcholine receptor antagonist
252	L-BSO	BRD-A47706533	-91.44	Glutathione transferase inhibitor
253	Dinoprostone	BRD-K26521938	-91.34	Prostanoid receptor agonist
254	GR-144053	BRD-K12120659	-91.31	Integrin antagonist
255	O-2050	BRD-K02590140	-91.29	Cannabinoid receptor antagonist
256	bis-tyrphostin	BRD-K32906660	-91.25	EGFR inhibitor
257	ITE	BRD-K60298136	-91.16	Aryl hydrocarbon receptor agonist
258	Nevirapine	BRD-K15502390	-91.15	Reverse transcriptase inhibitor
259	GR-235	BRD-K26674531	-91.08	Estrogen receptor agonist, FXR antagonist, Progesterone receptor agonist
260	Latrunculin-b	BRD-A19248578	-91.08	Actin polymerization inhibitor, Unidentified pharmacological activity
261	AR-C133057XX	BRD-K40892394	-91.08	Nitric oxide synthase inhibitor
262	Temefos	BRD-K51805276	-90.87	Cholinesterase inhibitor
263	Ilomastat	BRD-K51662849	-90.81	Matrix metalloprotease inhibitor
264	SID-26681509	BRD-K08417745	-90.75	Cathepsin inhibitor
265	Formestane	BRD-A31801025	-90.66	Aromatase inhibitor
266	Iproniazid	BRD-K88568253	-90.6	Monoamine oxidase inhibitor
267	Buphenine	BRD-A36267905	-90.46	Adrenergic receptor agonist
268	Desipramine	BRD-K60762818	-90.43	Tricyclic antidepressant
269	Tyrphostin-46	BRD-K60184833	-90.39	Tyrosine kinase inhibitor
270	RS-67506	BRD-K50018155	-90.29	Serotonin receptor partial agonist
271	BRD-K34437622	BRD-K34437622	-90.15	Thymidylate synthase inhibitor
272	Rotenonic-acid	BRD-K34330170	-90.11	Retinoid receptor antagonist
273	PIK-75	BRD-M16762496	-90.1	DNA protein kinase inhibitor, PI3K inhibitor
274	Zacopride	BRD-A65615053	-90.01	Serotonin receptor antagonist
275	Etifenin	BRD-K63979671	-90.00	Compound used in hepatobiliary scans of the liver

Table S4. Composition of four modules mediating host cell response during SARS-CoV2 infection

Module (# of proteins)	Dominant pathways/pr ocesses	Host cell proteins (gene names) in the module
Viral entry (27 proteins)	Endocytosis, lysosome pathway	Scavenger receptor class B member 1 (SCARB1); V-type proton ATPase subunit S1 (ATP6AP1); AP-3 complex subunit β -1 (AP3B1); NPC intracellular cholesterol transporter 2 (NPC2); integrin β -1 (ITGB1); Ras-related protein Rab-8A (RAB8A); AP-2 complex subunit α -2 (AP2A2); 1-phosphatidylinositol 3-phosphate 5-kinase (PIKFYVE); transforming protein RhoA (RHOA); Ras-related protein Rab-10 (RAB10); angiotensin-converting enzyme 2 (ACE2); AP-2 complex subunit mu (AP2M1); V-type proton ATPase catalytic subunit A (ATP6V1A); E3 ubiquitin-protein ligase NRDP1 (RNF41); charged multivesicular body protein 2a (CHMP2A); cathepsin B (CTSB); WASH complex subunit 4 (WASHC4); TMPRSS2; Ras-related protein Rab-7a (RAB7A); α -galactosidase A (GLA); spartin (SPART); cathepsin L1 (CTSL); palmitoyl-protein thioesterase 1 (PPT1); ADP-ribosylation factor 6 (ARF6); Ras-related protein Rab-5C (RAB5C); sialidase-1 (NEU1); two pore Ca^{2+} channel protein 2 (TPC2)
Viral replication and translation (45 proteins)	DNA replication, RNA transport, RNA degradation, protein processing in ER protein export	Nuclear pore glycoprotein p62 (NUP62); endoplasmic reticulum lectin 1 (ERLEC1); nuclear pore complex protein Nup214 (NUP214); eukaryotic translation initiation factor 4E type 2 (EIF4E2); 60S ribosomal protein L36 (RPL36); vesicular integral-membrane protein VIP36 (LMAN2); exosome complex component RRP40 (EXOSC3); nucleoporin p54 (NUP54); wolframin (WFS1); DNA primase large subunit (PRIM2); signal recognition particle subunit SRP72 (SRP72); nucleotide exchange factor SIL1 (SIL1); regulator of nonsense transcripts 1 (UPF1); selenoprotein S (SELENOS); DNA polymerase α catalytic subunit (POLA1); nuclear pore complex protein Nup88 (NUP88); protein OS-9 (OS9); hypoxia up-regulated protein 1 (HYOU1); mRNA export factor (RAE1); E3 ubiquitin-protein ligase RBX1 (RBX1); exosome complex component RRP4 (EXOSC2); mitochondrial small ribosomal subunit protein uS2m (MRPS2); nuclear pore complex protein Nup98-Nup96 (NUP98); 26S proteasome non-ATPase regulatory subunit 8 (PSMD8); peptide-N (4)- (N-acetyl- β -glucosaminyl)asparagine amidase (NGLY1); nucleoporin p58 (NUP58); ERO1-like protein β (ERO1B); ER degradation-enhancing α -mannosidase-like protein 3 (EDEM3); mitochondrial small ribosomal subunit protein uS5m (MRPS5); DNA primase small subunit (PRIM1); nuclear pore membrane glycoprotein 210 (NUP210); elongin-C (ELOC); signal recognition particle 54 kDa protein (SRP54); elongin-B (ELOB); UDP-glucose:glycoprotein glucosyltransferase 2 (UGGT2); exosome complex component RRP46 (EXOSC5); inosine-5'-monophosphate dehydrogenase 2 (IMPDH2); polyadenylate-binding protein 4 (PABPC4); exosome complex component RRP43 (EXOSC8); DNA polymerase α subunit B (POLA2); signal recognition particle 19 kDa protein (SRP19); pre-mRNA-splicing factor SLU7 (SLU7); cullin-2 (CUL2); mannosyl-oligosaccharide glucosidase (MOGS); polyadenylate-binding protein 1 (PABPC)
Regulation and signaling (27 proteins)	Ras signaling, autophagy, AMPK signaling, mTOR signaling, PI3K-AKT signaling and insulin signaling	Interleukin-6 receptor subunit α (IL6R); PIK3CA; Ras-related protein Rab-8A (RAB8A); Ras-related protein Ral-A (RALA); mTOR; serine/threonine-protein kinase TBK1 (TBK1); AKT1; NFkB1; guanine nucleotide-binding protein G (I)/G (S)/G (O) subunit γ -5 (GNG5); eukaryotic translation initiation factor 4E type 2 (EIF4E2); cAMP-dependent protein kinase type II- α regulatory subunit (PRKAR2A); Ras-related protein Rab-2A (RAB2A); MYD88; V-type proton ATPase catalytic subunit A (ATP6V1A); collagen α -1 (VI) chain (COL6A1); Ras-related protein Rab-14 (RAB14); MAPK1; RHOA; RAB10; cAMP-dependent protein kinase type II- β regulatory subunit (PRKAR2B); integrin β -1 (ITGB1); guanine nucleotide-binding protein G (I)/G (S)/G (T) subunit β -1 (GNB1); ARF6; RAB5C; evolutionarily conserved signaling intermediate in Toll pathway (ECSIT); cAMP-dependent protein kinase catalytic subunit α (PRKACA); NFATC1

Immune response (32 proteins)	Interferon-, TLR-, chemokine-, NFkB-, RIG-like receptor-, B-cell receptor-, T cell receptor- and HIF-1- signaling	Myeloid differentiation primary response protein MyD88 (MYD88); MAPK1; STAT3; cullin-2 (CUL2); heme oxygenase 1 (HMOX1); ELOB; receptor-interacting serine/threonine-protein kinase 1 (RIPK1); interleukin-17 receptor A (IL17RA); casein kinase II subunit β (CSNK2B); serine/threonine-protein kinase mTOR (MTOR); inhibin β E chain (INHBE); cAMP-dependent protein kinase catalytic subunit α (PRKACA); guanine nucleotide-binding protein G (I)/G (S)/G (T) subunit β -1 (GNB1); NLR family member X1 (NLRX1); ELKS/Rab6-interacting/CAST family member 1 (ERC1); RHOA; growth/differentiation factor 15 (GDF15); serine/threonine-protein kinase TBK1 (TBK1); IL6R; AKT1; casein kinase II subunit α (CSNK2A2); guanine nucleotide-binding protein G (I)/G (S)/G (O) subunit γ -5 (GNG5); NFATC1; TANK-binding kinase 1-binding protein 1 (TBKBP1); PIK3CA; cathepsin B (CTSB); E3 ubiquitin-protein ligase RBX1 (RBX1); NFkB1; ELOC; eukaryotic translation initiation factor 4E type 2 (EIF4E2); tissue-type plasminogen activator (PLAT); ARF6
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Table S5. Top-ranking 64 compounds involved in four disease modules, rank-ordered by the proximity of the corresponding targets to the disease modules (*)

Viral entry			Viral replication & translation		
Index	Compound name	z-score	Index	Compound name	z-score
1	SN-38	-2.97E+00	1	Methimazole	-3.93E+00
2	Hexylresorcinol	-1.87E+00	2	Mefenamic acid	-2.62E+00
3	GSK-1904529A	-1.79E+00	3	Fludarabine	-2.50E+00
4	Linsitinib	-1.79E+00	4	TGX-221	-1.87E+00
5	Sphingosine	-1.48E+00	5	Ibuprofen	-1.50E+00
6	Semaxanib	-1.09E+00	6	Razoxane	-1.38E+00
7	Azathioprine	-1.08E+00	7	Somatostatin	-8.50E-01
8	Imipramine	-8.18E-01	8	NU-7441	-8.39E-01
9	KU-55933	-7.96E-01	9	AS-605240	-7.83E-01
10	Mesoridazine	-7.43E-01	10	Leflunomide	-7.80E-01
11	Alisertib	-7.13E-01	11	NU-7026 (LY-293646)	-6.66E-01
12	Salmeterol	-6.89E-01	12	Aspirin	-6.62E-01
13	Terbutaline	-6.89E-01	13	Tolazoline	-4.83E-01
14	NBI-27914	-6.56E-01	14	Clobenpropit	-4.83E-01
15	Desoxycorticosterone	-6.45E-01	15	JNJ-16259685	-4.79E-01
16	GR-127935	-6.45E-01	16	VU-0415374-1	-4.79E-01
17	Terfenadine	-4.98E-01	17	NBI-27914	-4.79E-01
18	Dactolisib	-4.57E-01	18	Ponalrestat	-4.72E-01
19	JNJ-16259685	-4.48E-01	19	Brompheniramine	-2.93E-01
20	VU-0415374-1	-4.48E-01	20	Oxybutynin	-2.44E-01
21	SCH-23390	-4.46E-01	21	Ipratropium	-2.44E-01
22	Ezetimibe	-4.42E-01	22	Procyclidine	-2.44E-01
23	Brompheniramine	-4.39E-01	23	Hyoscyamine	-2.44E-01
24	Desipramine	-4.03E-01	24	Metixene	-2.44E-01
25	Oxybutynin	-3.61E-01	25	Rescinnamine	-2.28E-01
Cell signaling & regulation			Immune response		
Index	Compound name	z-score	Index	Compound name	z-score
1	PKC β -inhibitor	-4.10E+00	1	Fostamatinib	-5.16E+00
2	Dactolisib	-3.91E+00	2	NVP-TAE684	-4.47E+00
3	Fostamatinib	-3.48E+00	3	PKC β -inhibitor	-4.37E+00
4	NVP-TAE684	-3.24E+00	4	Bosutinib	-3.59E+00
5	Wortmannin	-3.19E+00	5	Wortmannin	-3.29E+00
6	PDE-V-Inhibitor II	-2.83E+00	6	WHI-P154 (JAK3-Inhibitor-II)	-3.04E+00
7	TPCA-1	-2.56E+00	7	TPCA-1	-3.04E+00
8	STO-609	-2.50E+00	8	Dactolisib	-2.88E+00
9	Bosutinib	-2.39E+00	9	NU-7441	-2.77E+00
10	Benidipine	-2.37E+00	10	PDE-V-Inhibitor II	-2.68E+00
11	Dipyridamole	-2.22E+00	11	Benidipine	-2.32E+00
12	SCH-23390	-2.00E+00	12	Dipyridamole	-2.06E+00
13	PI-103	-1.92E+00	13	Semaxanib	-2.06E+00
14	WHI-P154 (JAK3-Inhibitor-II)	-1.88E+00	14	AS-605240	-1.89E+00
15	AS-605240	-1.88E+00	15	KU-0063794	-1.87E+00
16	NU-7441	-1.81E+00	16	Temsirolimus	-1.87E+00
17	Alisertib	-1.80E+00	17	AZD-8055	-1.87E+00

(*)

18	KU-0063794	-1.79E+00	18	STO-609	-1.84E+00
19	Temsirolimus	-1.79E+00	19	PI-103	-1.81E+00
20	AZD-8055	-1.79E+00	20	Pimozide	-1.79E+00
21	Torin-1	-1.72E+00	21	SCH-23390	-1.70E+00
22	Semaxanib	-1.66E+00	22	Torin-1	-1.69E+00
23	Reserpine	-1.54E+00	23	Reserpine	-1.65E+00
24	Telmisartan	-1.48E+00	24	Leflunomide	-1.58E+00
25	Terfenadine	-1.36E+00	25	Aspirin	-1.40E+00

highlighted compounds/drugs have been experimentally tested. z-score is a measure of proximity, the lower scores indicating closer proximity. 25 compounds with the lowest proximity score are listed for each module. Several compounds participate in multiple modules resulting in 64 distinct compounds in the listed four modules.

Table S6A Grouping of 64 potentially antiviral compounds/drugs into clusters based on their interaction patterns with their targets (*)

Cluster index	Index	Compound name	PubChem ID	DrugBank ID
1	1	Ipratropium	657309	DB00332
	2	Terfenadine	5405	DB00342
	3	Brompheniramine	6834	DB00835
	4	Metixene	4167	DB00340
	5	Oxybutynin	4634	DB01062
	6	Procyclidine	4919	DB00387
	7	Hyoscyamine	154417	DB00424
2	8	Desipramine	2995	DB01151
	9	Imipramine	3696	DB00458
	10	Mesoridazine	4078	DB00933
	11	SCH-23390	5018	NA
	12	Pimozide	16362	DB01100
	13	Desoxycorticosterone	6166	NA
	14	GR-127935	107780	NA
3	15	AZD-8055	25262965	DB12774
	16	KU-0063794	16736978	NA
	17	Temsirolimus	6918289	DB06287
4	18	Wortmannin	312145	DB08059
	19	Torin-1	49836027	NA
	20	Dactolisib	11977753	NA
	21	PI-103	9884685	NA
	22	AS-605240	5289247	DB04769
	23	NU-7441	11327430	NA
	24	TGX-221	9907093	NA
5	25	GSK-1904529A	25124816	NA
	26	Linsitinib	11640390	NA
6	27	Salmeterol	5152	DB00938
	28	Terbutaline	5403	DB00871
7	29	STO-609	3467590	NA
	30	Bosutinib	5328940	DB06616
	31	Fostamatinib	11671467	DB12010
	32	NVP-TAE684	16038120	NA
	33	PKC β -inhibitor	6419755	NA
	34	WHI-P154 (JAK3-Inhibitor-II)	3795	NA
	35	Semaxanib	5329098	NA
	36	TPCA-1	9903786	NA
8	37	Tolazoline	5504	DB00797
	38	Clobenpropit	2790	NA
9	39	NU-7026 (LY-293646)	9860529	NA
10	40	SN-38	104842	DB05482
	41	Hexylresorcinol	3610	DB11254
11	42	Ponalrestat	5278	NA
	43	Aspirin	2244	DB00945
	44	Mefenamic acid	4044	DB00784
	45	Ibuprofen	3672	DB01050
12	46	Alisertib	24771867	DB05220
13	47	JNJ-16259685	11313361	NA
	48	VU-0415374-1	46869940	NA
14	49	PDE-V-Inhibitor II	9844109	NA
	50	Dipyridamole	3108	DB00975
15	51	Telmisartan	65999	DB00966
16	52	Leflunomide	3899	DB01097

17	53	Methimazole	1349907	DB00763
18	54	Sphingosine	5280335	DB03203
19	55	Somatostatin	16129681	DB09099
20	56	Razoxane	30623	NA
21	57	Fludarabine	657237	DB01073
22	58	Reserpine	5770	DB00206
23	59	Benidipine	656668	DB09231
24	60	Ezetimibe	150311	DB00973
25	61	NBI-27914	176157	NA
26	62	KU-55933	5278396	NA
27	63	Azathioprine	2265	DB00993
28	64	Rescinnamine	5280954	DB01180

* 13 compounds highlighted in yellow are prioritized after our analysis.

Table S6B. Grouping of 163 potential modulators of hyperinflammatory response into clusters based on their interaction patterns with their targets (*)

Cluster index	Index	Compound name	PubChem ID	DrugBank ID
1	1	Chlorprothixene	667467	DB01239
	2	Olanzapine	4585	DB00334
	3	Amoxapine	2170	DB00543
	4	Desipramine	2995	DB01151
	5	Trifluoperazine	5566	DB00831
	6	Maprotiline	4011	DB00934
	7	Promazine	4926	DB00420
	8	Ipsapirone	56971	NA
	9	Trazodone	5533	DB00656
	10	Nefazodone	4449	DB01149
	11	Zuclopenthixol	5311507	DB01624
	12	Cisapride	2769	DB00604
	13	Fluphenazine	3372	DB00623
	14	Lisuride	28864	DB00589
	15	Bromocriptine	31101	DB01200
	16	Piribedil	4850	DB12478
	17	Thiopropazine	9429	DB01622
	18	Quinpirole	54562	NA
	19	Pirenperone	4847	NA
	20	Ketanserin	3822	DB12465
	21	Latrepirdine	197033	DB11725
	22	Cyclazosin	132266	NA
	23	Midodrine	4195	DB00211
	24	Nor-binaltorphimine	5480230	NA
	25	EMD-386088	10131112	NA
	26	Dopamine	681	DB00988
	27	Azelastine	2267	DB00972
	28	Loratadine	3957	DB00455
	29	Verapamil	2520	DB00661
	30	Naftopidil	4418	DB12092
	31	Clonidine	2803	DB00575
	32	Alfuzosin	2092	DB00346
	33	Clebopride	2780	DB13511
	34	U-99194	5626	NA
2	35	Mepyramine	4992	DB06691
	36	Chlorphenamine	2725	DB01114
	37	Dicycloverine	3042	DB00804

	38	Oxybutynin	4634	DB01062
	39	Otenzepad	107867	NA
	40	Tolterodine	443879	DB01036
	41	Profenamine	3290	DB00392
	42	Xaliproden	NA	DB06393
	43	Alverine	3678	DB01616
	44	Bupropion	444	DB01156
	45	Indatraline	126280	NA
3	46	Sertraline	68617	DB01104
	47	Alprenolol	2119	DB00866
	48	ICI-89406	123686	NA
	49	Bisoprolol	2405	DB00612
4	50	Carteolol	2583	DB00521
	51	Clarithromycin	84029	DB01211
5	52	Bepridil	2351	DB01244
	53	Fipronil	3352	NA
	54	CGS-20625	163844	NA
	55	Topiramate	5284627	DB00273
6	56	Chlordiazepoxide	2712	DB00475
	57	Saracatinib	10302451	DB11805
	58	HY-11007	5311510	NA
	59	Dasatinib	3062316	DB01254
	60	Fostamatinib	11671467	DB12010
	61	TG-101348 (Fedratinib)	16722836	DB12500
	62	PLX-4720	24180719	DB06999
	63	TPCA-1	9903786	NA
	64	DMBI	5353593	NA
	65	Orantinib	5329099	DB12072
	66	D-64406	5330535	NA
7	67	WZ-4002	44607530	NA
	68	bis-tyrphostin	5329255	NA
	69	JAK3-Inhibitor-II	3795	NA
	70	TGX-221	9907093	NA
8	71	AZD-6482	44137675	DB14980
	72	GDC-0941 (Pictilisib)	17755052	DB11663
	73	PI-103	9884685	NA
	74	AZD-8055	25262965	DB12774
9	75	Roscovitine (Seliciclib)	160355	DB06195
	76	CGP-60474	644215	NA
10	77	Milrinone	4197	DB00235
	78	Anagrelide	2182	DB00261
	79	Hexamethylene	1794	NA
11	80	FIT	84008	NA
	81	Loperamide	3955	DB00836
	82	BRL-52537	6603740	NA
	83	Nicotine	89594	DB00184
12	84	Zacopride	108182	NA
	85	Metoclopramide	4168	DB01233
	86	m-chlorophenylbiguanide	1354	NA
	87	Palonosetron	6337614	DB00377
	88	Alosetron	2099	DB00969
	89	Flutamide	3397	DB00499
	90	Danazol	28417	DB01406
	91	Norgestimate	6540478	DB00957
	92	Oxybenzone	4632	DB01428
	93	α -estradiol	68570	NA
	94	Diethylstilbestrol	448537	DB00255

	95	Estradiol	5757	DB00783
	96	Testosterone	6013	DB00624
	97	Ticlopidine	5472	DB00208
	98	Nifedipine	4485	DB01115
	99	Nimodipine	4497	DB00393
	100	Spironolactone	5833	DB00421
	101	Liothyronine	5920	DB00279
	102	CITCO	9600409	NA
13	103	Piperine	638024	DB12582
	104	Phenelzine	3675	DB00780
	105	Iproniazid	3748	DB04818
	106	Selegiline	26757	DB01037
	107	Auraptene	1550607	NA
14	108	Atorvastatin	60823	DB01076
	109	Pravastatin	54687	DB00175
15	110	Exemestane	60198	DB00990
	111	Formestane	11273	DB08905
16	112	Felbamate	3331	DB00949
	113	Cycloserine	6234	DB00260
	114	Gavestinel	6450546	DB06741
	115	RO-25-6981	6604887	NA
17	116	EHNA	3206	NA
	117	SCH-442416	10668061	NA
18	118	Bromfenac	60726	DB00963
	119	DUP-697	3177	NA
	120	Dexketoprofen	667550	DB09214
	121	Oxaprozin	4614	DB00991
	122	Phenothiazine	7108	DB11447
	123	Triptolide	107985	DB12025
	124	Pyrazinamide	1046	DB00339
19	125	SCH-28080	108137	NA
	126	Pantoprazole	4679	DB00213
20	127	BIIB021	16736529	DB12359
	128	Geldanamycin	5288382	DB02424
21	129	STO-609	3467590	NA
22	130	Mafenide	3998	DB06795
23	131	AR-C133057XX	9797857	DB07002
24	132	Buphenine (Nyldrin)	4567	DB06152
25	133	AICA-ribonucleotide	65110	DB01700
26	134	Valproic acid	3121	DB00313
27	135	Iodophenpropit	3035746	NA
28	136	Retinol (Vitamin A)	445354	DB00162
29	137	Sildenafil	5212	DB00203
30	138	MK-2206	24964624	NA
31	139	KI-16425	10367662	NA
32	140	Dinoprostone	5280360	DB00917
33	141	BI-78D3	2747117	NA
34	142	Y-27632	448042	DB08756
35	143	SB-216763	176158	NA
36	144	Linsitinib	11640390	NA
37	145	PF-04217903	17754438	DB12848
38	146	Mepacrine	237	DB01103
39	147	Dicyclohexylurea	4277	NA
40	148	Pirfenidone	40632	DB04951
41	149	Dichloroacetic acid	6597	DB08809

42	150	MLN-4924 (Pevonedistat)	16720766	DB11759
43	151	Thenoyltrifluoroacetone	5601	DB04795
44	152	Navitoclax	24978538	DB12340
45	153	Daunorubicin	30323	DB00694
46	154	UNC-0321	46901937	NA
47	155	Isoliquiritigenin	638278	DB03285
48	156	PCA-4248	4698	NA
49	157	Pyroxamide	4996	DB12847
50	158	Rucaparib	9931954	DB12332
51	159	Ilomastat	132519	DB02255
52	160	Latrunculin-b	6436219	DB08080
53	161	Nicorandil	47528	DB09220
54	162	Z-prolyl-prolinal	122623	DB03535
55	163	BRD-K63784565	97226	DB12385

** The 24 compounds highlighted in yellow are prioritized based on the cluster analysis*

- 1 UniProt, C. UniProt: a worldwide hub of protein knowledge. *Nucleic Acids Res* **47**, D506-D515, doi:10.1093/nar/gky1049 (2019).