nature reviews microbiology

https://doi.org/10.1038/s41579-024-01036-y

Review article

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COVID-19 drug discovery and treatment options

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SUPPLEMENTARY TABLE 1 | **Representative virus-targeting therapeutic candidates for COVID-19.**

Targets	Drug class	Examples	Antiviral mechanism	Pre-clinical antiviral data
(A) Spike protein				
S1 subunit	mAb and nanobodies	Amubarvimab/romlusevimab Bamlanivimab-etesevimab Bebtelovimab Casirivimab-imdevimab Regdanvimab Sotrovimab Tixagevimab/cilgavimab 10-40	Targets the RBD and non-RBD regions of spike to inhibit virus entry into host cells.	*In vitro:* potently ↓ viral load and virus titers with EC_{50} in nM range. *In vivo:* ↓ clinical signs, respiratory tract viral load, virus titers, and tissue pathology in various animal models. Antiviral effects against different variants are variable[1,2].
	Convalescent plasma	Convalescent plasma	Plasma from recovered COVID-19 patients containing high-titer neutralizing anti-SARS-CoV-2 antibodies.	*In vivo:* passive immunization ↓ nasal and lung viral loads in Syrian hamsters and rhesus macaques[3-5].
	Aptamers	nCoV-S1-Apt1 to Apt6 RBD-PB6	Binds with S1 to inhibit spike-ACE2 interaction.	*In vitro:* EC_{50}: 0.1-0.2μM (HEK293T-hACE2-TMPRSS2 cells)[6,7].
	Miniprotein inhibitors	AHB1 & 2 LCB1 to 5	Binds with RBD to block spike-ACE2 interaction.	*In vitro:* EC_{50}: 24pM to 35nM VeroE6 cells)[8].
	Naturally occurring alkaloid	Cepharanthine	Inhibits spike-ACE2 binding to prevent viral entry into host cells.	*In vitro:* EC_{50}: 0.98μmol/L (VeroE6 cells)[9,10].

S2 subunit	Indole derivate	Umifenovir	Influenza drug that binds with SARS-CoV-2 S2 membrane fusion domain to ↓ viral fusion and entry.	*In vitro:* EC_{50}: 4.11μM (VeroE6 cells)[11,12].
	HIV protease inhibitors	Cobicistat	HIV protease inhibitor (darunavir-cobicistat) that inhibits SARS-CoV-2 spike-mediated fusion.	*In vitro:* EC_{50}: <8.76μM (cobicistat in VeroE6, Calu-3, and T84 cells) and is synergistic with remdesivir. *In vivo:* ↓ body weight loss and lung viral load and virus titer in Syrian hamsters[13].
	Peptides	$SARS_{HRC}$-PEG and related peptides EK1 and related peptides P9R and related peptides	Antiviral peptides that inhibit fusion of SARS-CoV-2 spike-mediated fusion.	*In vitro:* potently ↓ viral load and virus titers with IC_{50} in nM range. *In vivo:* ↓ respiratory tract viral load, virus titers, tissue pathology, and/or transmission in various animal models[14-18].
S1/S2 subunits	DARPin	Ensovibep (MP0420) MP0423	Binds to multiple epitopes on the spike protein S1 and/or S2 subunits to inhibit virus entry into host cells.	*In vitro:* EC_{50}: <10ng/ml (VeroE6 cells). *In vivo:* ↑ survival and ↓ lung viral load, virus titers, and tissue pathology in Roborovski dwarf hamsters[19].
	Salicylanilide derivative	Niclosamide DWRX2003	Anthelminthic that inhibits SARS-CoV-2 replication by ↓ TMEM16-mediated syncytium formation and/or other mechanisms.	*In vitro:* EC_{50}: 0.28-0.34μM (Vero and VeroE6 cells). *In vivo:* ↓viral load and inflammation in lung tissues of ferrets[20-22].
	Lectins	H84T-banana lectin (BanLec)	Binds to high-mannose glycans on spike protein to prevent virus entry into host cells.	*In vitro:* EC_{50}: <0.02μM (VeroE6 cells). *In vivo:* ↓ respiratory tract viral load, virus titer, and tissue pathology in hamsters[23].
		FRIL	Binds to complex-type glycans on spike protein.	*In vitro:* EC_{50}: <0.01μM (VeroE6 cells)[24].
		Griffithsin	Binds to high mannose glycans on spike protein to prevent virus entry into host cells.	*In vitro:* EC_{50}: <0.05μM (VeroE6 cells). *In vivo:* ↓ viral load and virus titer in mice[25,26].

(B) Viral enzymes				
PL^{pro}	CoV PL^{pro} inhibitors	F0213	Potential "pan-CoV" PL^{pro} inhibitor that competitively inhibits the PL^{pro} of SARS-CoV-2 and other CoVs via binding with the 157K amino acid residue.	*In vitro:* EC_{50}: 7.4μmol/L against SARS-CoV-2 PL^{pro}. *In vivo:* oral or IP F0213 ↓ lung viral load, virus titers, viral antigen expression, and tissue pathology in hamsters[27].
		GRL-0617	SARS-CoV inhibitor that also inhibits SARS-CoV-2 PL^{pro}.	*In vitro:* EC_{50}: 3.18μmol/L (VeroE6 cells)[28,29].
		rac3j, rac3k, and rac5c	SARS-CoV inhibitors that also inhibit SARS-CoV-2 PL^{pro}.	*In vitro:* ↓ SARS-CoV-2 replication (Vero cells)[30].
	Other repositioned drugs	6-thioguanine	Guanine analog used in the treatment of leukemia that inhibits SARS-CoV-2 PL^{pro}.	*In vitro*: EC_{50}: 2.13μM (VeroE6 cells)[31].
		Cryptotanshinone	Natural quinone compound and STAT-3 inhibitor that inhibits SARS-CoV-2 PL^{pro}.	*In vitro*: EC_{50}: 0.70μmol/L (VeroE6 cells)[28].
		Sepantronium bromide (YM155)	Survivin inhibitor that inhibits SARS-CoV-2 PL^{pro}.	*In vitro*: EC_{50}: 0.17μmol/L (VeroE6 cells)[28].
		Tanshinone I	Tanshinone that inhibits SARS-CoV-2 PL^{pro}.	*In vitro*: EC_{50}: 2.26μmol/L (VeroE6 cells)[28].
M^{pro}	CoV M^{pro} inhibitors	Nirmatrelir-ritonavir (PF-07321332)	Inhibits M^{pro} of SARS-CoV-2 and other CoVs. Lufotrelvir (PF-07304814) is a related intravenous SARS-CoV-2 M^{pro} inhibitor.	*In vitro:* "pan-coronaviral" activity against human-pathogenic CoVs in M^{pro} enzymatic inhibition and CPE inhibition assays (EC_{50}: <0.08μM in VeroE6s, A549-hACE2, and human bronchial epithelial cells). *In vivo:* ↓ weight loss, virus titer, and tissue pathology in BALB/c mice infected with mouse-adapted SARS-CoV-2[32].
		13b	Inhibits M^{pro} of SARS-CoV-2 and other	*In vitro:* EC_{50}: <5.0μM (Calu-3 cells)[33].

	CoVs.	
ALG-097431	Inhibits M^{pro} of SARS-CoV-2 and other CoVs.	*In vitro:* inhibits SARS-CoV-2 (EC_{50}: 0.2µM), HCoV-OC43, and HCoV-229E in A549-hACE2, HeLa, and Huh-7 cells, respectively. *In vivo:* ↓ lung viral load and virus titer in Syrian hamsters[34].
ASC-11	Inhibits SARS-CoV-2 M^{pro}.	*In vitro:* EC_{90}: 0.005µM (VeroE6 cells)[35].
EDP-235	Inhibits SARS-CoV-2 M^{pro}.	*In vitro:* EC_{90}: 0.033µM (VeroE6 cells)[35,36].
Ensitrelvir (S-217622)	Inhibits SARS-CoV-2 M^{pro}.	*In vitro:* "pan-coronaviral" activity against SARS-CoV-2 (EC_{50}: <0.5µM in VeroE6-TMPRSS2 cells) and other human-pathogenic CoVs[37]. *In vivo:* ↓ respiratory tract virus titer in mice and hamsters[37-39].
GC373 GC376	Feline CoV M^{pro} inhibitors that also inhibit SARS-CoV-2 M^{pro}.	*In vitro:* EC_{50}: 1.50µM (GC373) and 0.90 (GC376) (VeroE6 cells)[40].
GDI-4405	Inhibits SARS-CoV-2 M^{pro}.	*In vitro:* inhibits SARS-CoV-2 in multiple assays including in primary human-derived airway epithelial cells[41].
11a & 11b FB2001	Inhibits SARS-CoV-2 M^{pro}.	*In vitro:* EC_{50}: 0.53µM (VeroE6 cells)[42].
Leritrelvir (RAY1216)	Inhibits SARS-CoV-2 M^{pro}.	*In vitro:* EC_{50}: <200nM (VeroE6 cells)[43]. *In vivo:* ↑survival, ↓ lung viral titer, and tissue pathology in K18-hACE2 mice[43].
MI-09 MI-30	Novel bicycloproline-containing SARS-CoV-2 M^{pro} inhibitors.	*In vitro:* EC_{50}: <0.9µM (VeroE6 cells). *In vivo:* ↓ lung viral loads and tissue pathology in hACE2 mice[44].
PBI-0451	Inhibits SARS-CoV-2 M^{pro}.	*In vitro:* EC_{90}: 32nM (VeroE6 cells)[45].

		PF-00835231	SARS-CoV M^{pro} inhibitor that also inhibits SARS-CoV-2 M^{pro}.	*In vitro:* EC_{50}: 0.221μM (A549-ACE2 cells)[46].
		N3	Michael acceptor inhibitor that inhibits M^{pro} of SARS-CoV-2 and other CoVs.	*In vitro:* "pan-coronaviral" activity against SARS-CoV-2 (EC_{50}: 16.77μM in VeroE6 cells) and other human-pathogenic CoVs[47].
		Simnotrelvir-ritonavir (SIM0417)	Inhibits SARS-CoV-2 M^{pro}.	*In vitro:* EC_{50}: 43nM (VeroE6 cells)[48]. *In vivo:* ↓ body weight loss, lung virus titer, and tissue pathology in K18-hACE2 mice[48].
		Y180	Inhibits SARS-CoV-2 M^{pro}.	*In vitro:* EC_{50}: <0.04μM (VeroE6-TMPRSS2 cells). *In vivo:* ↑survival and ↓ body weight loss, lung viral load, virus titer, and tissue pathology in K18-hACE2 mice[49].
	HCV protease inhibitors	Boceprevir Ciluprevir Narlaprevir Telaprevir	HCV protease inhibitors that may also inhibit SARS-CoV-2 M^{pro}.	*In vitro:* EC_{50}: 11.552μM (telaprevir in VeroE6 cells)[50,51].
	HIV protease inhibitors	Atazanavir	HIV protease inhibitor (atazanavir-ritonavir) that also inhibits SARS-CoV-2 M^{pro}.	*In vitro:* EC_{50}: <0.5μM (atazanavir in Calu-3 cells)[52]. *In vivo:* ↑survival and ↓ body weight loss, lung viral load, and tissue pathology in K18-hACE2 mice[53].
		Lopinavir	HIV protease inhibitor (lopinavir-ritonavir) that also inhibits SARS-CoV-2 M^{pro}.	*In vitro:* EC_{50}: 11.6μM (lopinavir in VeroE6 cells)[54]. *In vivo:* ↓ clinical scores but no significant ↓ nasal wash viral load in ferrets[55].
	Other repositioned drugs	Emodin	An anthraquinone that inhibits SARS-CoV-2 M^{pro}.	*In vitro:* EC_{50}: <32.00μM (Vero and Calu-3 cells)[56].
RdRp	Remdesivir and related	Remdesivir (GS-5734) and its active	Broad-spectrum nucleoside analog viral RdRp inhibitor.	*In vitro:* EC_{50}: 0.77μM (VeroE6 cells)[57]. *In vivo:* ↓ clinical signs, lung infiltrates, viral

compounds	metabolite GS-441524		loads, virus titers, and tissue pathology in rhesus macaques[58].
	ATV006	Oral derivate of GS-441524 (parent nucleoside of remdesivir) viral RdRp inhibitor.	*In vitro:* EC_{50}: <2.00μM (VeroE6 and Huh7cells). *In vivo:* oral ATV006 ↓ lung viral loads, virus titer, and tissue pathology in mice[59].
	GS-621763	Oral prodrug of GS-441524 (parent nucleoside of remdesivir) viral RdRp inhibitor.	*In vitro:* EC_{50}: 0.11-0.73μM (VeroE6 cells). *In vivo:* ↓ clinical signs, respiratory tract viral load and virus titers, and transmission in ferrets[60].
	ODBG-P-RVn	Oral prodrug of GS-441524 (parent nucleoside of remdesivir) viral RdRp inhibitor.	*In vitro:* EC_{50}: <0.30μM (VeroE6, Calu-3, Huh-7.5, Caco-2, and human pluripotent stem cell-derived lung cells)[61]. *In vivo:* achieved therapeutic levels in plasma above EC_{90} for SARS-CoV-2 in Syrian hamsters[62].
	Mindeudesivir (JT001; VV116)	Oral derivate of GS-441524 (parent nucleoside of remdesivir) viral RdRp inhibitor.	*In vitro:* EC_{50}: 0.24μM (VeroE6 cells)[63]. *In vivo:* ↓ active against SARS-CoV-2 WT and variants in mice[64].
Other broad-spectrum RdRp inhibitors	Galidesivir (BCX4430)	Broad-spectrum nucleoside analog viral RdRp inhibitor.	*In vitro:* EC_{90}: <20.00μM (Vero76 and Caco2 cells). *In vivo:* ↓ weight loss, viral burden, and tissue pathology in Syrian hamsters[65].
	Molnupiravir (EIDD-2801 or MK-4482)	Oral prodrug of the broad-spectrum ribonucleoside analog NHC; induces mutations in the replication of viral RdRp.	*In vitro:* EC_{50}: <0.5μM (A549-hACE2 and Calu-3 cells)[66]. *In vivo:* ↓ lung viral load, virus titers, and tissue pathology in mice implanted with human lung tissue and Syrian hamsters, and ↓ transmission in ferrets[67-70].
	Ribavirin	Broad-spectrum nucleoside analog viral RdRp inhibitor.	*In vitro:* EC_{50}: 109.50μM[57].

	Triazavirin	Broad-spectrum nucleoside analog viral RdRp inhibitor that may also inhibit SARS-CoV-2 RdRp and M^{pro}.	*In silico:* potential SARS-CoV-2 M^{pro} inhibitor[71].
HCV inhibitors	Bemnifosbuvir (AT-527, RO7496998)	HCV nucleotide analog viral RdRp inhibitor that also inhibits SARS-CoV-2 RdRp.	*In vitro:* EC_{90}: 0.53μM[72].
	Sofosbuvir	HCV NS5B inhibitor that inhibits SARS-CoV-2 RdRp.	*In vitro:* EC_{50}: 5.1 to >10.0μM (VeroE6, Huh7, and Calu-3 cells)[73].
HIV inhibitors	Azvudine	HIV RdRp inhibitor that also inhibits SARS-CoV-2 RdRp and may also have immunomodulatory effects.	*In vitro:* inhibits replication of SARS-CoV-2 (EC_{50}: 4.31μM in VeroE6 cells) and HCoV-OC43 (1.2μM in H460 cells). - *In vivo:* ↓ respiratory tract and blood viral load, lung viral antigen expression, and lung tissue pathology in rhesus macaques[74].
	Tenofovir	HIV and HBV nucleotide analog RdRp inhibitor (tenofovir-emtricitabine) that also inhibits SARS-CoV-2 RdRp.	*In vivo:* ↓ clinical signs and nasal wash virus titers in ferrets[55,75].
Influenza inhibitors	Enisamium (FAV00A)	Isonicotinic acid derivative anti-influenza drug that inhibits SARS-CoV-2 RdRp.	*In vitro:* EC_{50}: 1200μM in Caco2 cells[76].
	Favipiravir	Anti-influenza nucleoside analog viral RdRp inhibitor that also inhibits SARS-CoV-2 RdRp.	*In vitro:* EC_{50}: 61.88μM[57]. *In vivo:* ↓ lung viral load, virus titers, and tissue pathology in Syrian hamsters[77].
Other repositioned drugs	Omipalisib	A PI3K/mTOR inhibitor that is predicted to inhibit SARS-CoV-2 RdRp.	*In vitro:* EC_{50}: <0.50μM (Vero and Calu-3 cells)[56].
	Tipifarnib	A farnesyltransferase inhibitor that is predicted to inhibit SARS-CoV-2 RdRp.	*In vitro:* EC_{50}: <12.00μM (Vero and Calu-3 cells)[56].
siRNAs	C6G25S sLNP-siUC7	siRNAs (with or without sLNPs) that target SARS-CoV-2 RdRp.	*In vitro:* EC_{50}: <0.1nM. *In vivo:* intravenous sLNP-siUC7, inhaled

		siR-7-EM/KK-46		C6G25S, and inhaled siR-7-EM/KK-46 ↓ lung viral load, virus titers, and tissue pathology in K18-hACE2 mice and Syrian hamsters[78-80].
Helicase	Helicase inhibitors	Ranitidine bismuth citrate	Anti-*Helicobacter pylori* infection and peptic ulcer disease drug that inhibits SARS-CoV-2 helicase.	*In vitro:* EC_{50}: 2.3μM (VeroE6 cells). *In vivo:* ↓ clinical signs, and lung viral load, virus titer, and tissue pathology in Syrian hamsters[81].
		FPA-124	AKT inhibitor that inhibits SARS-CoV-2 helicase.	*In vitro:* EC_{50}: 14μM (VeroE6 cells)[82].
		Myricetin	Flavonoid that inhibits SARS-CoV-2 helicase.	*In vitro:* EC_{50}: 32μM (VeroE6 cells)[82].
		Suramin	Anti-parasitic that inhibits SARS-CoV-2 helicase.	*In vitro:* EC_{50}: 9.9μM (VeroE6 cells)[82].
		SSYA10-001	SARS-CoV helicase inhibitor that also inhibits SARS-CoV-2 helicase.	*In vitro:* EC_{50}: 81μM (VeroE6 cells)[82].
		sLNP-siHel2	siRNAs with sLNPs that target SARS-CoV-2 helicase.	*In vivo:* intravenous sLNP-siHel2 and inhaled C6G25S ↓ lung viral load, virus titers, and tissue pathology in K18-hACE2 mice[78].
Exonuclease	HCV inhibitors	Elbasivr Pibrentasvir Ombitasvir	Inhibit SARS-CoV-2 exonuclease.	*In vitro:* EC_{50}: 0.4-0.7μM (Calu-3 cells)[83].
Endoribonuclease	TPase inhibitor	Tipiracil	TPase inhibitor used in the treatment of colorectal cancer that inhibits SARS-CoV-2 SARS-CoV-2 endoribonuclease.	*In vitro:* inhibition of endoribonuclease activity but limited effect on viral replication (A549-hCE2 cells)[84].
2′-O-methyltransferase	Miscellaneous	Compound 11 Nsp10 peptides	*In silico* prediction of high binding affinities with SARS-CoV-2 2′-O-methyltransferase.	*In silico:* uncertain *in vitro* or *in vivo* antiviral activity[85,86].
Multiple enzymes	Antimycobacterial	Clofazimine	Inhibits SARS-CoV-2 helicase and	*In vitro*: EC_{50}: 0.31μM (VeroE6 cells).

			RdRp.	*In vivo:* ↓ lung viral load, virus titers, and tissue pathology in Syrian hamsters[87].
	HCV inhibitors	Simeprevir Grazoprevir Paritaprevir Vaniprevir	Inhibits SARS-CoV-2 M^{pro}, PL^{pro}, and/or RdRp.	*In vitro:* EC_{50}: 4.082μM (VeroE6 cells)[88,89].
		Daclatasvir Ledipasvir Velpatasvir	Inhibit SARS-CoV-2 RdRp and exonuclease.	*In vitro:* EC_{50}: 0.6-1.1μM (daclatasvir in VeroE6, Huh7, and Calu-3 cells)[73,74,83].
	Others	Carmofur Disulfiram Ebselen PX-12 Shikonin Tideglusib	Non-specific inhibition of SARS-CoV-2 PL^{pro}, M^{pro}, nsp13 ATPase, and/or nsp14 exoribonuclease.	*In vitro:* inhibits SARS-CoV-2 PL^{pro}, M^{pro}, nsp13 ATPase, and/or nsp14 exoribonuclease activities; EC_{50}: 24.30μM (carmofur in VeroE6 cells)[47,90-92].
(C) Other viral targets				
	Viroporin inhibitors	Amantadine Emodin Epigallocatechin Hexamethylene-amiloride Quercetin Xanthene	Inhibits SARS-CoV-2 envelope protein and other viroporins from inducing intracellular membrane remodelling to generate membrane vesicles as viral replication site and/or ion channel activities.	*In vitro:* EC_{50}: 83-119μM (amantadine in VeroE6 cells)[93-95].
	siRNAs	siORF1 (O1 to O3) siL (L1 to L3) siN (N1 to N11) siU (U1 to U3)	siRNA targeting different genomic and subgenomic RNAs of SARS-CoV-2.	*Ex vivo:* siORF1 (O3) ↓ viral load in *ex vivo* lung culture model[96,97].

Abbreviations: CXR, chest X-ray; DARPin, designated ankyrin repeat protein; FRIL, Flt3 receptor interacting lectin; HCV, hepatitis C virus; HIV, human immunodeficiency virus; M^{pro}, main protease; NHC, beta-D-N4-hydroxycytidine; PL^{pro}, papain-like protease; RdRp, RNA-dependent RNA polymerase; siRNA, small interfering RNA; sLNP, stealth lipid nanoparticle; TMEM16, transmembrane protein 16; TPase, thymidine phosphorylase.

SUPPLEMENTARY TABLE 2 | **Representative host-targeting therapeutic candidates for COVID-19.**

Target	Drug class	Examples	Antiviral mechanism	Pre-clinical antiviral data
(A) Host immune response				
Broad-spectrum	Alkaloid	Colchicine	Anti-mitotic drug that inhibits microtubule assembly and modulates multiple inflammatory pathways.	Clinical uses: inflammatory disorders such as gout, pericarditis, Behçet's disease, and familial Mediterranean fever. Uncertain *in vitro* and *in vivo* efficacy against SARS-CoV-2[98].
	Indole-imidazole derivative	Sabizabulin (VERU-111)	Novel bis-indole microtubule depolymerisation agent with anti-inflammatory and potentially antiviral effects.	*In vitro:* ↓ inflammatory cytokines in endotoxin-stimulated mouse spleen cells[99].
	Glucocorticoids	Dexamethasone Methylprednisolone Hydrocortisone	Systemic corticosteroids with broad-spectrum anti-inflammatory effects.	*In vivo:* combination of systemic methylprednisolone and remdesivir ↓ body weight loss, viral loads, and tissue inflammation in Syrian hamsters[100].
		Budesonide Ciclesonide	Inhaled corticosteroids that ↓ airway inflammation. Ciclesonide also targets SARS-CoV-2 nsp3 and/or nsp4 to inhibit viral replication.	*In vitro:* EC_{50}: 4.33μM (ciclesonide in Vero cells) and EC_{90}: 0.55μM in human bronchial tracheal epithelial cells[20,101].
Interferons				
Type I IFNs	Recombinant type I	Recombinant IFN-α	A family of cytokines with	Clinical uses: HBV and HCV infections (IFN-α)

	IFNs	Recombinant IFN-β	broad-spectrum antiviral activities.	and multiple sclerosis (IFN-β). *In vitro:* potent antiviral activity against SARS-CoV-2 alone or in combination with other antivirals[54,102]. *In vivo:* early use of intranasal IFN-α ↓weight loss, lung viral load and virus titers, and tissue damage in Syrian hamsters[103].
Type II IFNs	Antibodies against type II IFNs	Neutralizing antibody against IFN-γ	Neutralizing antibodies that block IFN-γ-mediated inflammation.	*In vitro:* IFN-γ ↑ viral replication in human colonic organoids[104]. *In vivo:* neutralizing antibodies against IFN-γ and TNF-α co-treatment ↑ survival and ↓ tissue damage of K18-hACE2 mice[105].
Type III IFNs	Recombinant type III IFNs	Recombinant IFN-λ	A family of cytokines with broad-spectrum antiviral activities.	*In vitro:* pegylated IFN-λ1 ↓ SARS-CoV-2 replication in primary human airway epithelial cells[106]. *In vivo:* early use of pegylated IFN-λ1 ↓ SARS-CoV-2 replication in mice[106]. Intranasal IFN-λ2 ↓ respiratory tract viral load, virus titers, and tissue damage in K18-hACE2 mice[107].
IFN inducers	Synthetic double-stranded RNA analogues	Poly(I:C)	TLR3/MDA5 synthetic agonist that potently induces IFN production.	*In vitro:* poly(I:C)-primed mesenchymal stem cells exhibit ↑ antiviral and immunomodulatory response pathways and ↑ expression of antiviral proteins (MX1, IFITM3, and OAS1). Addition of poly(I:C)-primed mesenchymal stem cells to COVID-19 patients' whole blood ↓ inflammatory neutrophils and ↑ M2 monocytes with enhanced phagocytic effector function[108]. *In vivo:* early use of intranasal poly(I:C) results in ↑ survival rate, ↓ viral loads, and ↓ lung and brain cytokine storm in K18-hACE2-transgenic mice[109].
Interleukins				

IL-1	IL-1 inhibitors	Anakinra Canakinumab	IL-1 receptor antagonist (eg: anakinra) and mAb (eg: canakinumab) that ↓ IL1-mediated immunopathologies.	Clinical uses: immune disorders such as rheumatoid arthritis, systemic juvenile idiopathic arthritis, Still's disease, and neonatal-onset multisystem inflammatory disease. Anakinra has been used to treat pediatric patients with MIS-C.
IL-6	IL-6 inhibitors	Sarilumab Siltuximab Tocilizumab	Anti-IL-6 receptor mAb (eg: tocilizumab and sarilumab) and anti-IL-6 mAb (eg: siltuximab) that ↓ IL6-mediated immunopathologies.	Clinical uses: immune disorders such as rheumatoid arthritis, CAR T-cell therapy-induced cytokine release syndrome, and Castleman disease. Tocilizumab and sarilumab may be used in combination of corticosteroids for treatment of COVID-19.
Other inflammatory mediators				
BET	BRD2 and BRD4 inhibitors	Mivebresib (ABBV-075) ABBV-744 Apabetalone (RVX-208) CPI-0610 dBET6 JQ-1 MZ1 SF2523	Inhibits BRD2 and BRD4-mediated regulation of gene transcription.	*In vitro:* EC_{50}: 1.52μM (SF2523 in Vero STAT1 KO cells)[110,111].
BTK	BTK inhibitors	Acalabrutinib Ibrutinib Zanubrutinib	Inhibits B-cell and macrophage activation, signalling, and development to ↓ immunopathologies.	Clinical uses: B-cell malignancies such as chronic lymphocytic leukemia and mantle cell lymphoma, and chronic GVHD. Uncertain *in vitro* and *in vivo* anti-SARS-CoV-2 efficacy.
JAK	JAK inhibitors	Baricitinib Ruxolitinib Tofacitinib	Interferes with phosphorylation of key proteins involved in the inflammatory response. Baricitinib may also ↓ clathrin-mediated endocytosis	Clinical uses: immune disorders such as rheumatoid arthritis, psoriatic arthritis, juvenile idiopathic arthritis, and ulcerative colitis, and hematological disorders such as myelofibrosis, polycythemia vera, and acute GVHD. Used in combination with remdesivir and/or

			of SARS-CoV-2[112].	corticosteroids. *In vivo:* baricitinb ↓ inflammation and pulmonary tissue pathologies in SARS-CoV-2-infected rhesus macaques[113].
Sigma-1 and -2 receptor	SSRI	Fluvoxamine	Reduces pro-inflammatory cytokine production through binding to sigma-1 receptor on immune cells; may also ↓ SARS-CoV-2 entry through inhibition of acid sphingomyelinase and ceramide-enriched membrane domain formation[114,115].	Clinical uses: depression and obsessive-compulsive disorder. Uncertain *in vitro* and *in vivo* efficacy against SARS-CoV-2.
		Chloroquine Clemastine Haloperiodol PB28 PD-144418 RS-PPCC	Perturbs sigma receptor-mediated cell stress response.	*In vitro:* ↓ viral antigen ± titer (VeroE6 cells)[116].
Histamine receptor	H_2 receptor antagonist	Famotidine	Inhibits histamine-induced TLR3 expression and cytokine release in SARS-CoV-2 infected cells.	Clinical uses: peptic ulcer disease and gastroesophageal reflux disease. *In vitro:* no effect on viral replication, but ↓ CCL-2 and IL-6 expression levels in SARS-CoV-2 infected cells[117].
GM-CSF	Anti-GM-CSF mAbs	Gimsilumab Lenzilumab Mavrilimumab Namilumab Otilimab	Blocks interaction between GM-CSF and its cell surface receptor or the intracellular signalling of GM-CSF to ↓ immunopathologies.	Uncertain *in vitro* and *in vivo* efficacy against SARS-CoV-2.
Complements	Complement inhibitors	AMY-101 (anti-C3) Eculizumab (anti-C5) Ravulizumab (anti-C5) Zilucoplan (anti-C5) Vilobelimab (anti-C5a)	Anti-complement mAbs and peptides that ↓ complement-mediated immunopathologies.	Clinical uses: myasthenia gravis, paroxysmal nocturnal hemoglobinuria[118-121].

TOP1	TOP1 inhibitors	Topotecan	Inhibits TOP1-mediated inflammation.	Clinical uses: chemotherapeutic agent for ovarian, cervical, and lung cancers. *In vitro:* ↓ SARS-CoV-2-induced inflammatory gene expression *In vivo:* ↓ inflammation in hamsters and ↑ survival in K18-hACE2 mice[122].
HMGB1	HMGB1 inhibitors	Glycyrrhizin	Inhibits HMGB1-mediated inflammatory response, lung ACE2 mRNA expression, and inhibits SARS-CoV-2 M^{pro}.	*In vitro:* EC_{50}: 0.44mg/mL (VeroE6 cells)[123,124].
HDAC2	HDAC inhibitors	Apicidin Belinostat Vorinostat Valproic acid	Inhibit HDAC2-mediated inflammatory and interferon response.	*In vitro:* ↓ ACE2 expression but uncertain effects on SARS-CoV-2 replication[116,125].
S1P	S1P receptor modulators and spingosine kinase inhibitors	Fingolimod Opaganib	Inhibits S1P synthesis and the associated inflammatory response.	Clinical uses: multiple sclerosis (fingolimod). *In vitro:* ↓ viral load in human bronchial epithelial cells[126].
(B) Host factors involved in the viral replication cycle				
Receptor				
ACE2	Recombinant soluble hACE2	ACE2-1-618-DDC-ABD hACE2 1-618	Act as decoys to compete with cell-bound ACE2 to ↓ spike-ACE2 binding.	*In vitro:* ↓ viral load of SARS-CoV-2 WT and variants and human kidney organoids[127]. *In vivo:* ↓ clinical scores, lung viral load and virus titers, and tissue damage in K18-hACE2-transgenic mice and Syrian hamsters[128,129].
	Bivalent ACE2-Fc	M81	Competes with cell-bound ACE2 and possesses robust	*In vitro:* cross-neutralizes SARS-CoV-2 WT and variants with low nM EC_{50}.

			Fc-effector functions, including antibody-dependent cellular cytotoxicity, phagocytosis, and complement deposition.	*In vivo:* ↑ survival and ↓ respiratory tract viral load in K18-hACE2-transgenic mice[130].
	Circulating extracellular vesicles expressing ACE2	evACE2	Act as decoys to compete with cell-bound ACE2 to ↓ spike-ACE2 binding.	*In vitro:* neutralizes SARS-CoV-2 WT and variants with about 80-fold higher potentcy than recombinant soluble ACE2. *In vivo:* intranasal evACE2 ↑ survival and ↓ lung viral load in K18-hACE2-transgenic mice [114].
	PPAR-α agonist	Fenofibrate	Destabilizes RBD-ACE2 binding and may reverse alterations in lipid metabolism induced by SARS-CoV-2.	*In vitro:* EC_{50}: 7-14μM (Vero cells)[131].
Attachment factors and/or co-receptors				
HSPGs	Sulfated glycans	LMWH Fucoidans Mucopolysaccharide polysulfate Pentosan polysulfate Unfractionated heparin	Competitive inhibitors of heparan sulfate.	Clinical uses: anticoagulation (heparin) and interstitial cystitis (pentosane polysulfate). *In vitro:* ↓ viral entry[132-135].
	Other inhibitors of HSPG-dependent endocytosis	BNTX Brilacidin Lactoferrin Mitoxantrone Piceatannol Raloxifene Sunitinib Tilorone	Directly inhibits heparan sulfate or disrupts actin network to indirectly inhibit heparan sulfate-assisted viral entry.	*In vitro:* ↓ viral entry and virus-induced CPE; EC_{50}: <23μM (brilacidin in Vero, Calu-3, Caco-2, Huh-7, and 293T-ACE2 cells)[132,136,137].
CD147 (basigin or	Humanized anti-	Meplazumab (HP6H8)	Inhibits CD147-mediated	Clinical uses: severe eosinophilic ashma,

EMMPRIN)	CD147 antibody		SARS-CoV-2 entry.	eosinophilic granulomatosis, and hypereosinophilic syndrome. *In vitro:* EC_{50}: 15.16μg/ml[138].
Entry				
Surface host proteases	Serine protease inhibitors	Camostat Nafaomstat Upamostat	Inhibits spike-TMPRSS2 binding to reduce TMPRSS2-mediated virus entry into host cells.	Clinical uses: chronic pancreatitis and reflux esophagitis. *In vitro:* EC_{50}: 2.2nM (HAE cells) to 22.50μM (nafamostat, VeroE6 cells)[57,139,140]. *In vivo:* intranasal nafamostat ↓ virus titers, weight loss, and mortality in K18-hACE2 mice[141].
	Peptidomimetics	N-0385	Inhibits TMPRSS-2-mediated virus entry into host cells.	*In vitro:* EC_{50}: 2.8nM (Calu-3 cells)[142]. *In vivo:* ↓ morbidity and mortality in K18-hACE2 mice[142].
	Kallikrein-related B1 inhibitor	Avoralstat	Inhibits TMPRSS-2-mediated virus entry into host cells.	*In vitro:* inhibits SARS-CoV-2 entry and replication in human airway epithelial cells[143]. *In vivo:* ↓ lung tissue viral titers and body weight loss in Ad5-hACE2-transduced BALB/c mice[143].
	Mucolytics	Bromhexine	Inhibits spike-TMPRSS2 binding of TMPRSS2 to reduce TMPRSS2-mediated virus entry into host cells.	*In vitro:* inhibits TMPRSS2 with EC_{50}: 0.75μM and SARS-CoV-2 entry in lung cells[144].
	Antiandrogens	Apalutamide Bicalutamide Enzalutamide	Inhibits transcriptional expression of TMPRSS2 to reduce TMPRSS2-mediated virus entry into host cells.	*In vivo:* ↓ TMPRSS2 levels in human lung cells and mouse lung[145].
Endosomal host	Adamantanes	Amantadine	Inhibits cathepsin L-mediated	*In vitro:* EC_{50}: 83-119μM (amantadine in

proteases			virus entry into host cells.	VeroE6 cells)[93]. *In vivo:* ↓ SARS-CoV-2 pseudovirus infection in hACE2 humanized mice[146].
	Cysteine protease inhibitor	Aloxistatin (E64d)	Inhibits cathepsin L-mediated virus entry into host cells.	*In vitro:* ↓ SARS-CoV-2 pseudovirus infection (293T-hACE2 cells)[147]. *In vivo:* ↓ SARS-CoV-2 pseudovirus infection in hACE2 humanized mice[146].
	Glycopeptides	Dalbavancin	Inhibits cathepsin L-mediated virus entry into host cells.	*In vitro:* EC_{50}: 12nM (VeroE6 cells). *In vivo:* ↓ viral load and pulmonary tissue pathologies in hACE2 mice and rhesus macaques[148].
	Selective cathepsin L inhibitors	SID 26681509	Inhibits cathepsin L-mediated virus entry into host cells.	*In vitro:* ↓ SARS-CoV-2 pseudovirus infection (293T-hACE2 cells)[147].
Other endosomal entry regulators	4-aminoquinolines	Chloroquine Hydroxychloroquine	Increases endosomal pH to inhibit fusion of SARS-CoV-2 with host cell membrane, glycosylation of ACE2, and transport of SARS-CoV-2 rom early endosomes to endolysosomes.	*In vitro:* EC_{50}: 1.13-7.36μM (chloroquine) and 4.06-12.96μM (hydroxychloroquine) (VeroE6 cells)[57,149]. *In vivo:* ↓ lung viral load and tissue pathology in hACE2 mice, but not in hamsters, ferrets, and rhesus macaques[55,150-152].
	Bis-benzylisoquinoline alkaloids	Berbamine	Endosomal acidification	*In vitro:* EC_{50}: 2.4μM (VeroE6 cells)[153].
	Cardiac glycosides	Bufalin Digoxin Ouabain	Inhibits Na^+/K^+-ATPase-mediated regulation of intracellular ion homeostasis and/or ATP1A1-mediated Src signalling[154].	*In vitro:* EC_{50}: <0.2μM (Vero and VeroE6 cells)[155-157].
	Macrolides	Bafilomycin A1	Endosomal acidification	*In vitro:* ↓ viral load (Vero, Huh-7, and 293T-hACE2 cells).

				In vivo: ↓ lung viral load and tissue pathology in hACE2 mice[150].
	Phenothiazines	Chlorpromazine	Inhibits viral entry through clathrin-mediated endocytosis.	*In vitro:* EC_{50}: 8.2μM (VeroE6 and A549-ACE2 cells)[158].
	PIK-fyve inhibitors	Apilimod Vacuolin-1 YM201636	Inhibits PIK-fyve-mediated synthesis of PI(3,5)P2 which regulates endosome maturation.	*In vitro:* ↓ SARS-CoV-2 pseudovirus entry (apilimod, 293/hACE2 cells)[147,159,160].
	RAB7A siRNA	*RAB7A* knockout	↓ viral entry by intracellular ACE2 sequestration through altered endosomal trafficking.	*In vitro:* ↓ cell surface expression and ↑ endosomal accumulation of ACE2[159].
	TPC2 antagonists	Naringenin Tetrandrine	Inhibits TPC2-mediated endolysosomal functions and virus entry.	*In vitro:* ↓ SARS-CoV-2-induced CPE (naringenin, VeroE6 cells) and pseudovirion entry (tetrandrine, 293/hACE2 cells)[147,162].
Other host proteases	Furin inhibitors	Agmatine Andrographolide BOS-981 and BOS-138 CMK Naphthofluorescein	Inhibits furin-mediated cleavage at the S1/S2 polybasic cleavage (PRRAR) site which is important for virus entry.	*In vitro:* ↓ viral load (EC_{50} of CMK: 0.057μM), CPE, spike cleavage and syncytia formation (VeroE6 and MK2 cells)[162-166].
	MT-MMP inhibitors	Incyclinide Prinomastat 20(R)-ginsenoside Rh2	Inhibits MT-MMP-mediated virus entry into host cells.	*In vitro:* ↓ viral load in Calu-3 and Caco-2 cells. *In vivo:* intranasal incyclinide or 20(R)-ginsenoside Rh2 ↓ lung viral load, virus titers, viral antigen expression, and tissue pathology in Syrian hamsters[167].
Translation and protein synthesis				
AP2M1	AP2M1 inhibitors	ACA	Inhibits AP2M1-YxxØ motif interaction-mediated	*In vitro:* broad-spectrum activity against SARS-CoV-2 and other CoVs, as well as multiple

			intracellular virus trafficking.	DNA and RNA families[168].
Translation elongation	Translation elongation inhibitors	Cycloheximide	Inhibits translation elongation.	*In vitro:* EC_{50}: 0.17μM (Caco-2 cells)[169].
40S ribosomal protein S14	40S ribosomal protein S14 inhibitors	Emetine	Inhibits 40S ribosomal protein S14.	*In vitro:* EC_{50}: 0.47μM (Caco-2 cells)[169].
eEF1A	eEF1A inhibitors	Plitidepsin Ternatin-4	Inhibits eEF1A-mediated mRNA translation, protein synthesis and viral replication.	Clinical use: multiple myeloma *In vitro:* EC_{50}: <0.8nM (plitidepsin in VeroE6 and 293T-hACE2 cells). *In vivo:* sc plitidepsin ↓ lung virus titer and tissue pathology in K18-hACE2 mice[116,170].
eIF4A	eIF4A inhibitor	Zotatifin	Inhibits eEF1A-mediated mRNA translation, protein synthesis and viral replication.	Clinical use: phase 1 clinical trial for cancer *In vitro:* EC_{50}: 0.037μM[116].
PI3K/AKT/ mTOR	PI3K/AKT/mTOR inhibitors	ASTEX Everolimus OSI-127 Rapamycin Temisirolimus	Inhibits PI3K/AKT/mTOR-mediated protein synthesis and viral replication.	*In vitro:* ↓ SARS-CoV-2 viral load (Vero, Calu-3, and 293T-ACE2 cells)[110,171-173].
Viral glycoprotein folding	Iminosugars	Celgosivir EB-0281 Miglustat MON-DNJ	Inhibits α-glucosidases I and II which are involved in the early stages of glycoprotein N-linked oligosaccharide processing in ER.	Clinical uses: HCV (celgosivir) and lysosome storage diseases (miglustat). *In vitro:* EC_{50}: 1μM (celgosivir, Huh7-hACE2 cells), 9.5μM (EB-0281, Calu-3 cells) and 45.2μM (miglustat, Calu-3 cells)[174,175].
Sec61	Sec61 inhibitors	PS3061	Inhibits Sec61-mediated protein biogenesis.	*In vitro:* ↓ virus titer (VeroE6 cells)[116].
UPR activation	Antibiotics	Clofoctol	Inhibits translation of viral RNA possibly through activation of UPR pathways	*In vitro:* EC_{50}: 12.41μM (Vero-81 cells)[176]. *In vivo:* intraperitoneal clofoctol ↓ lung virus titer and inflammation in K18-hACE2 mice[176].

Lipid and cholesterol biosynthesis				
ATP citrate lyase	ATP citrate lyase inhibitors	Bempedoic acid SB 204990	Inhibits the conversion of acetyl-CoA from citrate in the citrate induced *de novo* lipogenesis mini pathway within the tricarboxylic acid cycle.	Clinical use: hypercholesterolemia (bempedoic acid). *In vitro:* EC_{50}: 5-20μM for WT and variants of SARS-CoV-2. *In vivo:* IP SB 204990 ↓ viral load, virus titer, and viral antigen expression in hamsters[177].
DGAT	DGAT inhibitors	Xanthohumol	Inhibits DGAT-mediated lipid droplet formation.	*In vitro:* EC_{50}: 4.7μM (Caco-2 cells). *In vivo:* oral xanthohumol significantly reduces the viral loads, viral antigen expression, pro-inflammatory cytokines, and tissue pathology in Syrian hamsters[178].
Eicosanoids	PTGDR inhibitors	Asapiprant	Inhibits PTGDR-mediated eicosanoid signalling.	*In vivo:* ↑ survival and ↓ lung virus titers and tissue damage in mice infected with mouse-adapted SARS-CoV-2[179].
PIK3C3	PIK3C3 inhibitors	Autophinib ALLN PIK-III Compound-19	Increases cholesterol biosynthesis.	*In vitro:* ↓ viral load (A549-ACE2 cells)[161].
SREBPs	SREBP inhibitors	AM580 Tamibarotene	Inhibits SREBP-mediated lipogenesis essential for viral replication.	Clinical uses: acute promyelocytic leukemia *In vitro:* EC_{50}: 7.6μM (AM580 in VeroE6 cells)[54]. *In vivo:* inhaled tamibarotene ↓ clinical signs, lung viral load, virus titer, and tissue damage in Syrian hamsters[180].
Others				
Apoptosis	Caspase 6 inhibitors	z-VEID-fmk	Inhibits coronavirus nucleocapsid cleavage,	*In vitro:* EC_{50}: 3.3μM (Calu-3 cells). *In vivo:* ↓ lung viral load, virus titers, viral

			reduces IFN antagonism, and restricts virus replication.	antigens, and tissue damage in Syrian hamsters[181].
Cyclophilins	Cyclophilin inhibitors	Alisporivir Cyclosporine A	Interaction of cyclophilins with CoV nsp1 and the calcineurin-NFAT pathway.	Clinical uses: HCV (alisporivir) and immunosuppression (cyclosporin A). *In vitro:* EC_{50}: 0.46 µM (alisporivir in VeroE6 cells)[182].
Virus-induced senescence	Senolytics	Dasatinib-quercetin Fisetin Navitoclax	Selective elimination of virus-induced senescent cells.	*In vitro:* selectively eliminates virus-induced senescent cells. *In vivo:* ↑ survival and ↓ lung tissue damage in Roborovski dwarf hamsters and K18-hACE2 mice[183].
Uncertain	Avermectins	Ivermectin	Likely acts on multiple targets.	Clinical uses: nematode and ectoparasite infection/infestation. *In vitro:* EC_{50}: <10µM (VeroE6 cells)[184,185].
	Thiazolide	Nitazoxanide	Inhibition of proinflammatory cytokines and host enzymes to ↓ post-translational processing of viral proteins.	Clinical uses: *Cryptosporidium parvum* and *Giardia duodenalis* infections. *In vitro:* EC_{50}: 0.58-3.19 µM (VeroE6 and Caco-2 cells)[57]. *In vivo:* no significant viral load reduction in Syrian hamsters with suboptimal tissue concentrations of tizoxanide (the active metabolite of nitazoxanide) that were below the *in vitro* EC_{50}[186].

Abbreviations: ACA, N-(p-amylcinnamoyl)anthranilic acid; ARDS, acute respiratory distress syndrome; ASTEX, activated specialized tissue effector extracellular vesicles; ATP, adenosine triphosphate; BET, bromodomain and extraterminal; BRD2 and BRD4, bromodomain-containing proteins 2 and 4; BTK, Bruton's tyrosine kinase; CAR, chimeric antigen receptor; CD147; cluster of differentiation 147; CMK, decanoyl-RVKR-chloromethylketone; COPD, chronic obstructive pulmonary disease; CoV, coronavirus; CPE, cytopathic effects; DGAT, diacylglycerol acyltransferase; eEF1A, elongation factor-1A; eIF4A, eukaryotic initiation factor-4A; ER, endoplasmic reticulum; evACE2, extracellular vesicles expressing ACE2; GM-CSF, granulocyte-macrophage colony-stimulating factor; GVHD, graft-versus-host disease; hACE2, human angiotensin-converting enzyme 2; HAE, primary human airway epithelia; HBV, hepatitis B virus; HCV, hepatitis C virus; HDAC2, histone deacetylase 2; HDV, hepatitis D virus; HMGB1, high mobility group box 1; HSPGs, heparan sulfate proteoglycans; IFN, interferon; IFN, interferon; IL, interleukin; IP, intraperitoneal; JAK, Janus kinase; LMWH, low molecular weight heparin; mAb, monoclonal antibody; MEK/ERK, Ras/Raf/Mitogen-activated protein kinase/ERK kinase/extracellular-signal-regulated kinase; MIS-C, multisystem inflammatory syndrome; MMPRIN; extracellular matrix metalloproteinase induce; MMT-MMP, membrane-type matrix metalloproteinase; NF-κB, nuclear factor kappa B (NF-κB); NLRP3, nucleotide-binding oligomerization domain-, leucine-rich repeat-, and pyrin domain-containing protein 3; PI(3,5)P2, phosphatidyl-inositol-3,5-bisphosphate; PI3K/AKT/mTOR, phosphoinositide3-kinase/protein kinase B/mammalian target of rapamycin; PIK3C3, phosphatidylinositol 3-kinase catalytic

subunit type 3; PIK-fyve, phosphatidylinositol 3-phosphate 5-kinase; PTGDR, prostaglandin D_2 receptor; S1P, sphingosine-1-phosphate; sc, subcutaneous; SERMs; selective estrogen receptor modulators; SREBPs, sterol regulatory-element binding proteins; SSRI, selective serotonin reuptake inhibitor; TMPRSS2, transmembrane protease, serine 2; TOP1, topoisomerase 1; TPC2, two-pore channel 2; TRPMLs, transient receptor potential mucolipin channels; UPR, unfolded protein response.

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